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# HCV NS-3 Serine Protease Inhibitors

## Technical Field

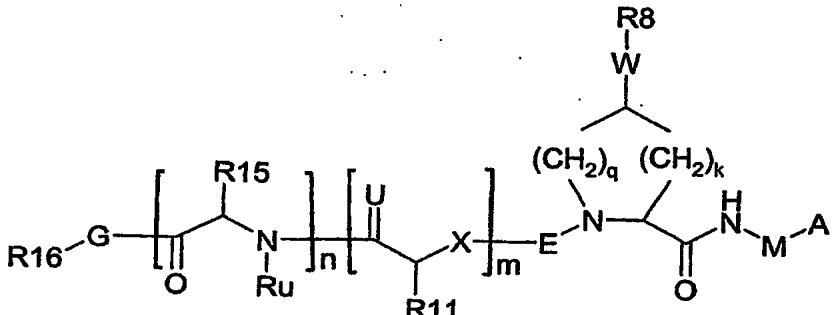
This invention relates to novel inhibitors of the NS3 serine protease of the flavivirus HCV and to methods for their use in the treatment or prophylaxis of HCV.

## Background Art

The NS3 serine protease of HCV is a multifunctional protein which contains a serine protease domain and a RNA helicase domain. The protease cofactor NS4A, which is a relatively small protein, is absolutely required for enhanced serine protease activity. The NS3 serine protease is essential in the viral lifecycle. From analysis of the substrate binding site as revealed by X-ray crystal structure, it has been shown that the binding site of the NS3 protease is remarkably shallow and solvent exposed making small molecule inhibitor design a challenge.

## Brief description of the invention

In accordance with a first aspect of the invention, there are provided compounds of the formula I:




(I)

wherein

A is $COOR^1$, $CONHSO_2R^2$, $CONHR^3$, or $CR^4R^{4'}$ wherein;

$R^1$ is hydrogen, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl;

$R^2$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl;

$R^3$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, -$OC_1$-$C_6$alkyl, -$OC_0$-$C_3$alkylcarbocyclyl, -$OC_0$-$C_3$alkylheterocyclyl;

$R^4$ is =O, halo, amino, or OH;

$R^{4'}$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl; wherein

$R^2$, $R^3$, and $R^{4'}$ are each optionally substituted with from 1 to 3 times with halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-$R_b$, Y-C(=O)$R_b$, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

where Y is independently a bond or $C_1$-$C_3$ alkyl;

Ra is independently H or $C_1$-$C_3$ alkyl;

Rb is independently H, $C_1$-$C_6$ alkyl, $C_0$-$C_3$ alkylcarbocyclyl or $C_0$-$C_3$heterocyclyl;

p is 1 or 2;

M is $CR^7R^{7'}$ or NRu;

$R^7$ is $C_1$-$C_6$alkyl, $C_1$-$C_3$ alkyl $C_3$-$C_7$cycloalkyl, or $C_2$-$C_6$alkenyl, any of which is optionally substituted with 1-3 halo atoms, amino or –SH;

$R^{7'}$ is H or taken together with $R^7$ to form a $C_3$-$C_6$ cycloalkyl ring optionally substituted with $R^{7'a}$ wherein;

$R^{7'a}$ is $C_1$-$C_6$ alkyl, $C_3$-$C_5$cycloalkyl, $C_2$-$C_6$ alkenyl or J; any of which may be optionally substituted with halo;

q is 0 to 3 and k is 0 to 3; where $q+k \geq 1$;

W is -$CH_2$-, -O-, -OC(=O)NH-, -OC(=O)-, -S-, –NH-, -$NR^{8'}$ , -$NHSO_2$-, -NHC(=O)NH- or -NHC(=O)-;

$R^8$ is a ring system containing 1 or 2 saturated or unsaturated rings each of which has 4-7 ring atoms and 0 to 2 hetero atoms selected from S, O and N, the ring system being optionally spaced from W by a $C_1$-$C_3$ alkyl group; or $R^8$ is $C_1$-$C_6$ alkyl, any of which $R^8$ groups can be optionally mono, di, or tri substituted with $R^9$, wherein

$R^9$ is independently halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-

$S(=O)_pNRaR_b$, Y-C(=O)$OR_b$, Y-NRaC(=O)$OR_b$; wherein the carbocyclyl or heterocyclyl is optionally substituted with $R^{10}$; wherein

$R^{10}$ is $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_6$alkoxy, amino optionally mono- or di- substituted with $C_1$-$C_6$-alkyl, sulfonyl, ($C_1$-$C_3$ alkyl)sulfonyl, $NO_2$, OH, SH, halo, haloalkyl, carboxyl, amide, ($C_1$-$C_3$alkyl)amide;

$R^{8'}$ is H, $C_1$-$C_3$alkyl;

E is -C(=O)-, -C(=S)-, -$S(=O)_2$-, -S=O-, -C=N-Rf;

Rf is H, -CN, -C(=O)NRaRb; -C(=O)$C_1$-$C_3$ alkyl

X is –NRx- where Rx is H, or $C_1$-$C_6$alkyl; or in the case where where E is –(C=O) X can also be –O- or -NRjNRj-;

wherein one of Rj is H, the other is H or J;

$R^{11}$ is H, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

when $R^{7'}$ taken together with $R^7$ forms a $C_3$-$C_6$ cycloalkyl, then one of Rj, Rx, Ry or $R^{11}$ can also be J;

J, if present, is a 3 to 10-membered saturated or unsaturated alkylene chain extending from the $R^7$/$R^{7'}$ cycloalkyl to Rj, Rx, Ry or $R^{11}$ to form a macrocycle, which chain is optionally interrupted by one to three heteroatoms independently selected from: -O-, -S- or -$NR^{12}$- wherein 0 to 3 carbon atoms in the chain are optionally substituted with $R^{14}$; wherein;

$R^{12}$ is H, $C_1$-$C_6$ alkyl, $C_3$-$C_6$cycloalkyl, or $COR^{13}$;

$R^{13}$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl;

$R^{14}$ is independently selected from H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ alkoxy, hydroxy, halo, amino, oxo, thio, or $C_1$-$C_6$ thioalkyl;

Ru is independently H or $C_1$-$C_3$ alkyl;

*m* is 0 or 1; *n* is 0 or 1;

U is O or is absent;

$R^{15}$ is H, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$ alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

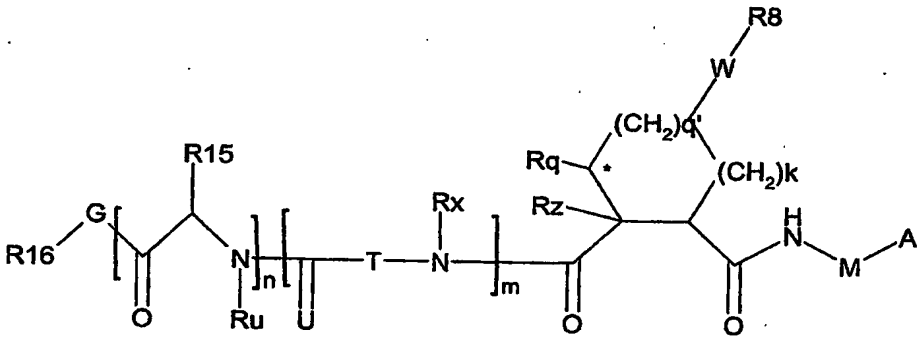
G is –O-, -NRy-, -NRjNRj-,

where Ry is H, $C_1$-$C_3$ alkyl or J;

$R^{16}$ is H; or $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

or a pharmaceutically acceptable salt or prodrug thereof.

A second aspect of the invention provides compounds of the formula VI:




VI

wherein

$R^7$, $R^{7'}$, $R^8$, $R^{11}$, $R^{15}$, $R^{16}$, Rj, Ru, Rx, Ry, A, G, k, m, n, U, M are as defined above;

q' is 0 or 1;

Rz is H, or together with the asterisked carbon forms an olefinic bond;

Rq is H or $C_1$-$C_4$-alkyl;

T is -$CHR^{11}$- or –NRd-, where Rd is H or $C_1$-$C_3$alkyl;

in the case where $R^7$ taken together with $R^{7'}$ forms a $C_3$-$C_6$ cycloalkyl, one of Rj, Rx, Ry, Rd or $R^{11}$ can be J;
J is a 5 to 10 membered saturated or unsaturated alkylene chain extending from the $R^7/R^{7'}$ cycloalkyl to Rd, Rj, Rx, Ry, or $R^{11}$ to form a macrocycle, which chain is otherwise as defined above;
and pharmaceutically acceptable salts and prodrugs thereof.

Without in any way wishing to be bound by theory, or the ascription of tentative binding modes for specific variables, the notional concepts P1, P2, P3 and P4 as used herein are provided for convenience only and have substantially their conventional meanings and denote those portions of the inhibitor believed to fill the S1, S2, S3 and S4 subsites respectively of the enzyme, where S1 is adjacent the cleavage site and S4 remote from the cleavage site. Regardless of binding mode, the components defined by Formula I, VI etc are intended to be within the scope of the invention. For example it is expected that capping group $R^{16}$-G may interact with the S3 and S4 subsites.

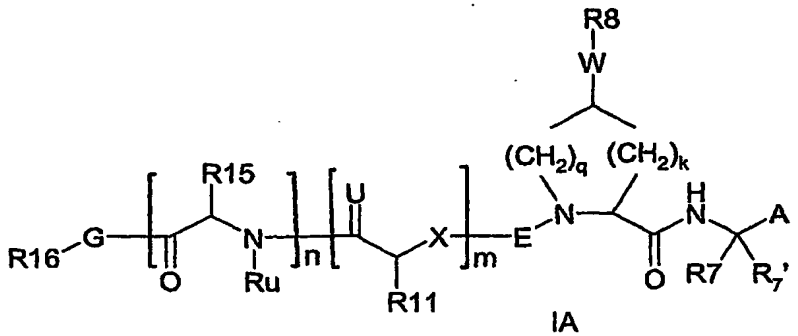
The compounds of the present invention, can be briefly represented as $R^{16}$-G-P4-P3-link-P2-P1, wherein P3 and/or P4 may be absent, and P1, P3 and P4 each represents a building block constituted of a derivative of a natural or unnatural amino acid, P2 is a cyclic residue and G and $R^{16}$ are capping groups. The link is a carbonyl or other function as defined for E. The P1 and P2 building blocks and the P3 and P4 building blocks are thus typically linked together by amide bonds whereas the P2 and P3 building blocks are linked through the above described link. The amide bonds are thereby typically reversed relative to each other on each side of the link in the compounds of the invention

Additional aspects of the invention include a pharmaceutical composition comprising a compound of the invention as defined above and a pharmaceutically acceptable carrier or diluent therefore.

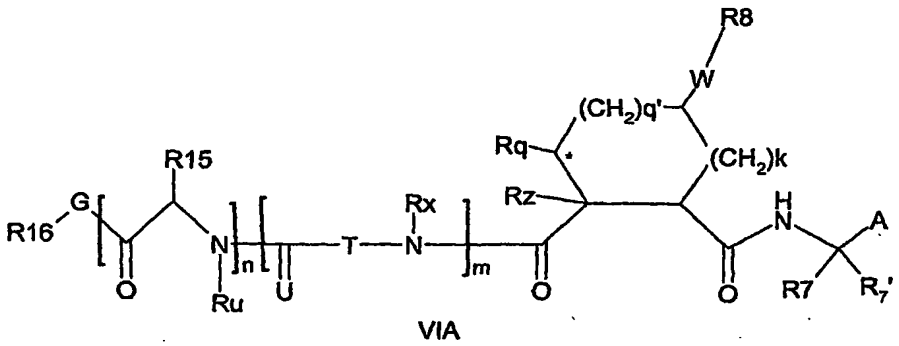
The compounds and compositions of the invention have utility in methods of medical treatment or prophylaxis of HCV infections in humans. Accordingly, a further aspect of the invention is the use of a compound as defined above in the manufacture of a medicament for the prophylaxis or treatment of flavivirus infections in humans or animals. Exemplary flavivirus include BVDV, dengue and especially HCV.

A preferred group of compounds of the invention comprises those wherein P1 represents a hydrazine derivative, that is M is NRu where Ru is typically H or $C_1$-$C_3$alkyl. Compounds wherein M is $CR^7R^{7'}$ constitute a further preferred aspect of the invention.

Preferred embodiments wherein M is $CR^7R^{7'}$ in formulae I and VI include formulae IA and VIA below:

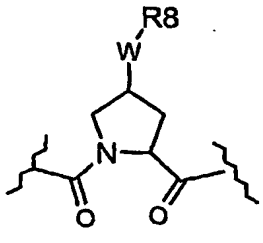



IA

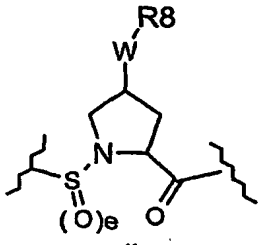



VIA

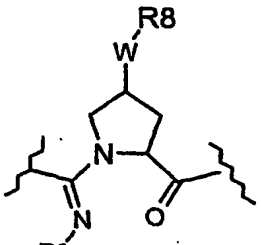
Preferred values for q and k in Formula I include 2:1, 2:2, 2:3, 3:2, 3:3, more preferably 1:2 and 1:0; and most preferably 1:1, in which case preferred compounds have the partial structure:




Ia




Ib

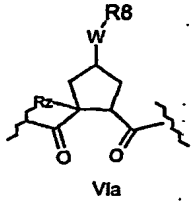



Ic

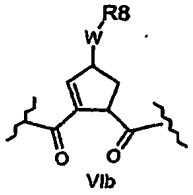
where e is 1 or 2.

It is currently preferred that E is –C(=O)- or –C=N-Rf, for example where Rf is -CN or-C(=O)$NH_2$

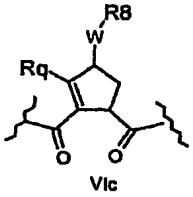
Preferred values for q' and k in formula VI include 1:1, 1:2, 1:3, 2:2, 2:3, more preferably 0:2 and 0:0; and most preferably 0:1, in which case preferred compounds have one of the partial structures:




VIa



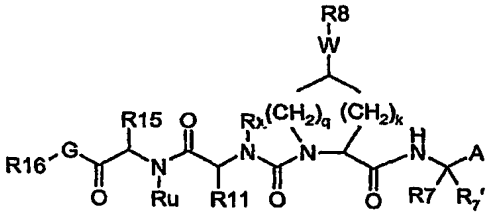

VIb



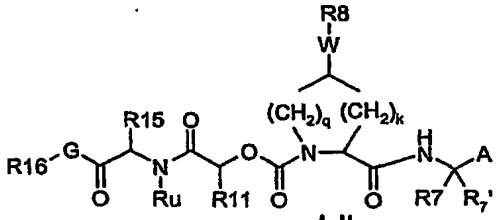

VIc

especially where Rz is H or Rq is H or methyl.

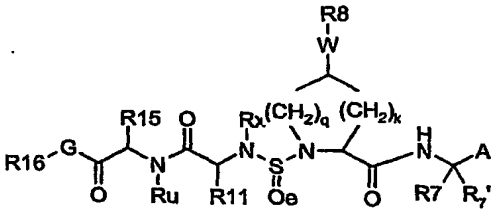
Compounds of the invention may comprise both a P3 and a P4 function, viz m and n are each 1. Favoured embodiments within formula I include formula Ida-Idd below:



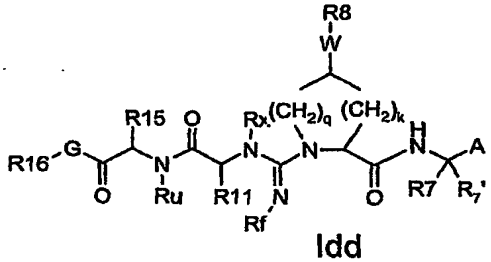
Ida



Idb



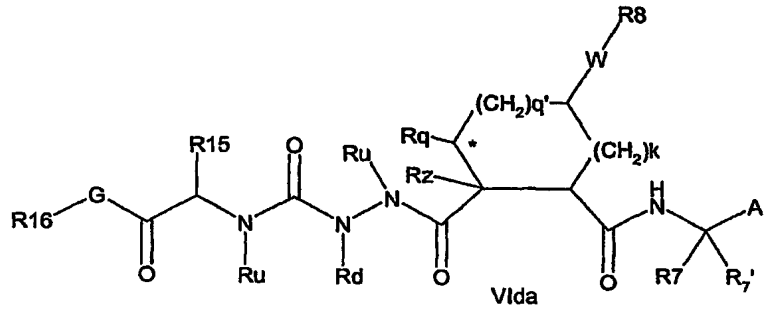
Idc



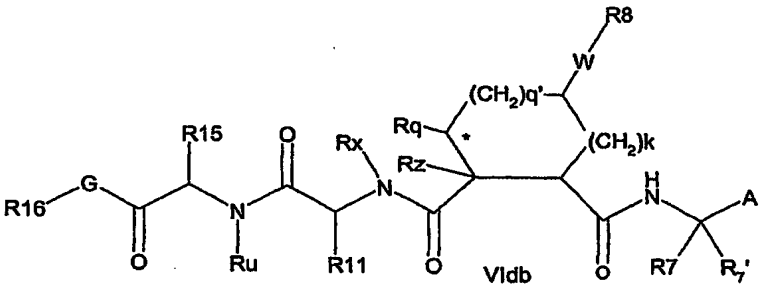
Idd

Alternative embodiments include the structures corresponding to Ida, Idb, Idc and Idd wherein M is NRu.

Favoured embodiments within Formula VI comprising both a P3 and P4 function include formula VIda-VIdb below:



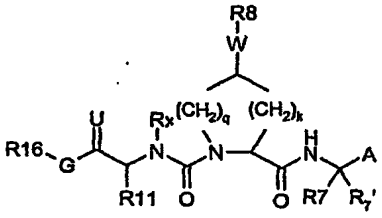

VIda



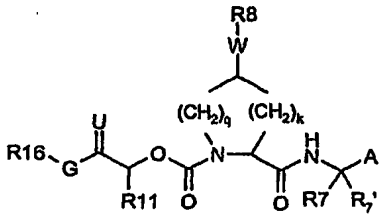

VIdb

Alternative embodiments include the structures corresponding to VIda, and VIdb wherein M is NRu.

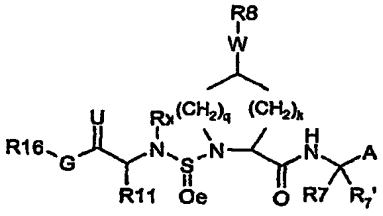
Alternative configurations of the compounds of the invention comprise a P3, but no P4 function, viz m is 1 and n is zero. Preferred embodiments within Formula I include formulae Iea-Iee below:



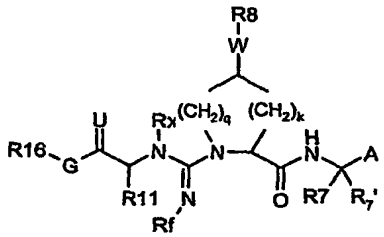
Iea



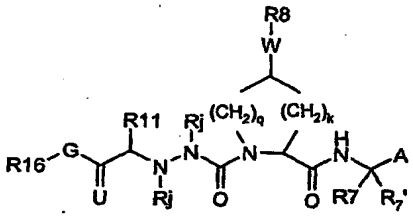
Ieb



Iec



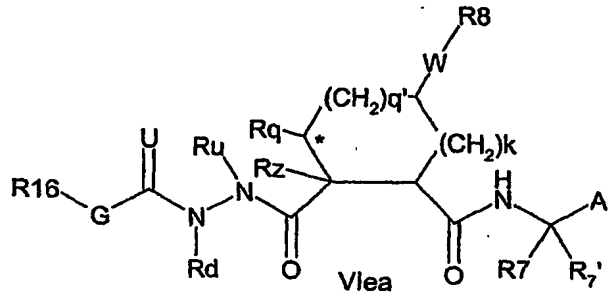
Ied



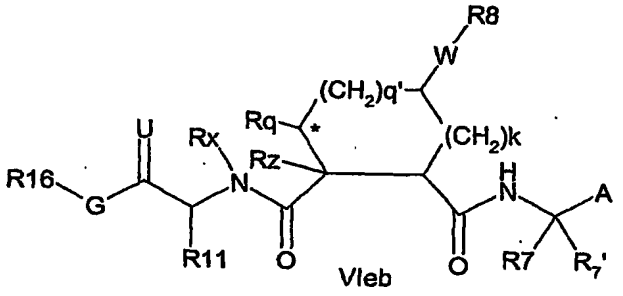
Iee

Alternative embodiments include the structures corresponding to Iea, Ieb, Iec, Ied and Iee wherein M is NRu.

Favoured embodiments within Formula VI comprising a P3, but no P4 include formula VIea-VIeb below:




Vlea

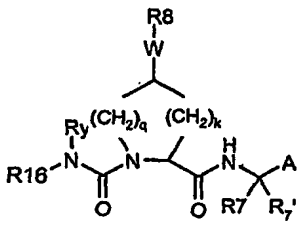



Vleb

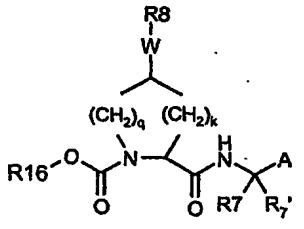
Alternative embodiments include the structures corresponding to Vlea and Vleb wherein M is NRu.

Still further alternative configurations of the compounds of the invention include those where m and n are zero and thus groups $R^{16}$-G about P2, but as mentioned above, the capping group R16-G may interact favourably with S3 and/or S4.

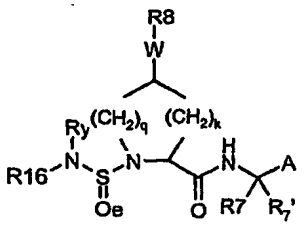
Favoured embodiments within Formula I include formulae Ifa-Ife below:



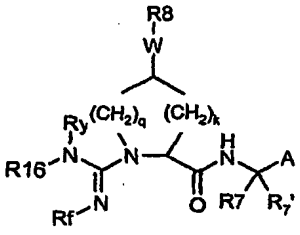

Ifa



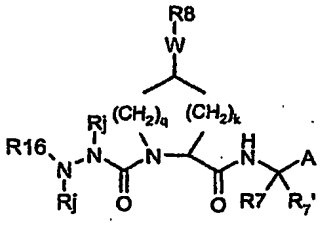

Ifb




Ifc



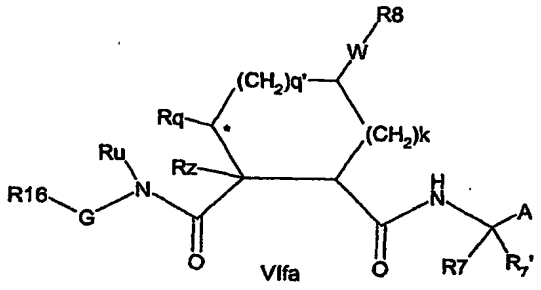

Ifd




Ife

Alternative embodiments include the structures corresponding to Ifa, Ifb, Ifc, Ife, and Ife wherein M is NRu.

Favoured embodiments within Formula VI wherein m and n are zero include those of formula VIfa below:



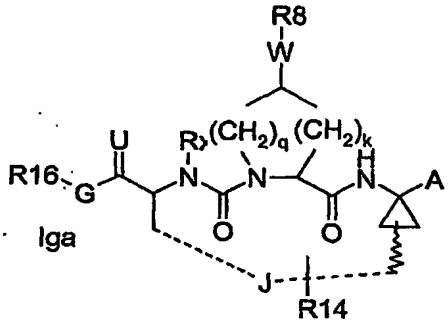

VIfa

Alternative embodiments include the structures corresponding to VIfa, wherein M is NRu.

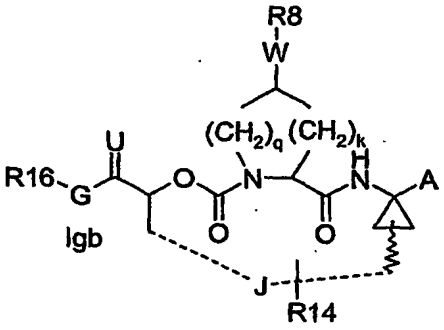
The compounds of the invention may comprise linear molecules, as depicted above. Alternatively, in embodiments wherein $R^7$ and $R^{7'}$ together define a spiro cycloalkyl group, such as spiro-cyclopropyl, the compounds of the invention may be configured

as macrocycles, wherein a linking group J extends between Rj, Rx, Ry or $R^{11}$ of formula I or Rj, Rx, Ry, Rd or $R^{11}$ of Formula VI.

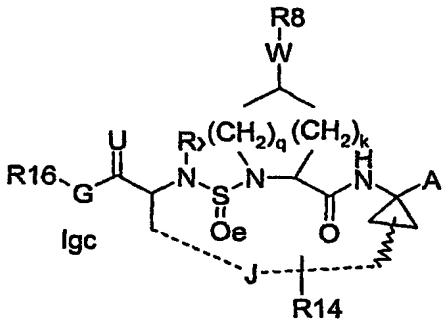
Favoured embodiments of such macrocyclic structures within formula I wherein m is 0 and n is 1 include those of Formulae Iga-Igd below:



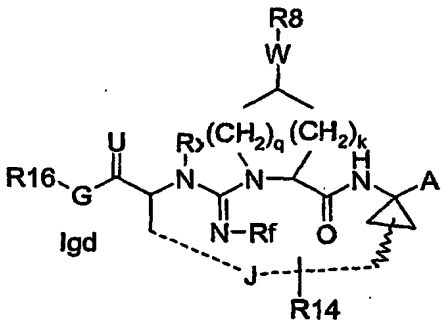

Iga




Igb

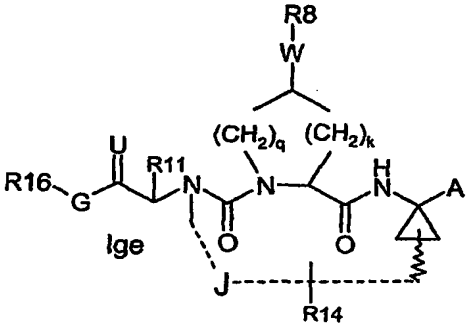



Igc

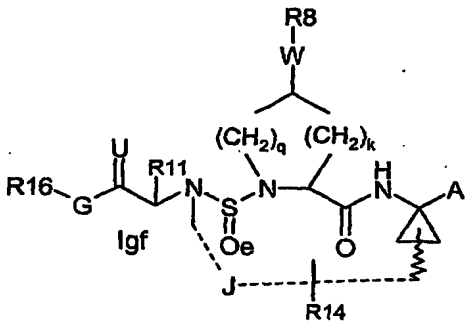



Igd

Additional favoured embodiments of such macrocyclic structures within formula I wherein m is 0 and n is 1 include those of Formulae Ige-Igf below:

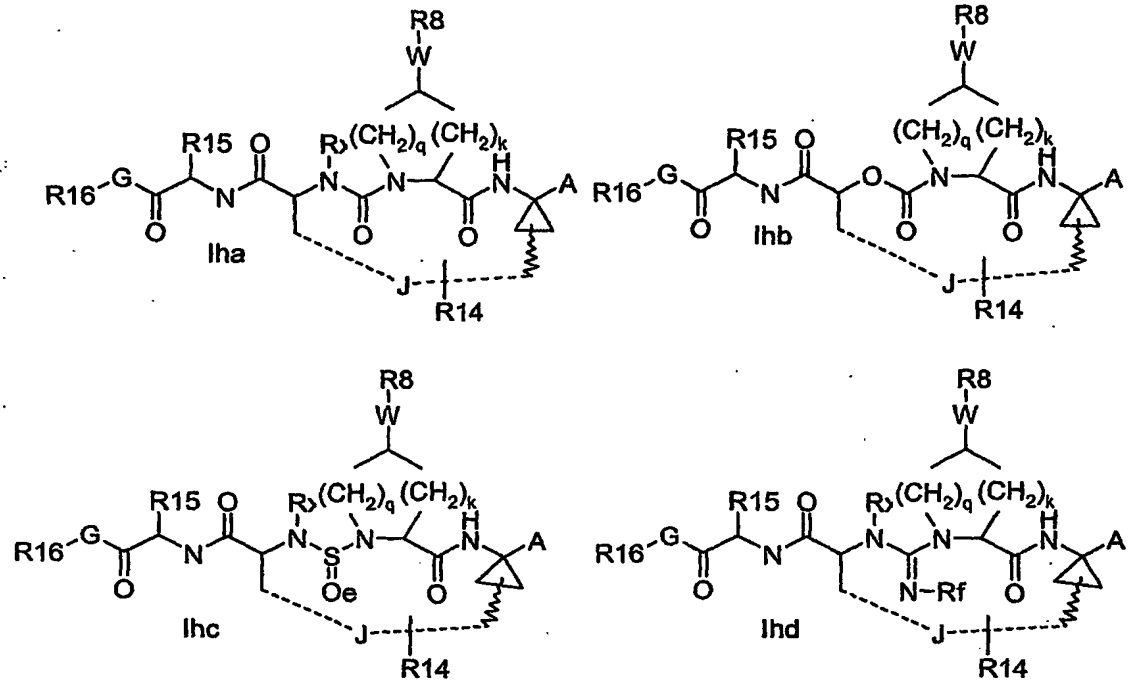



Ige

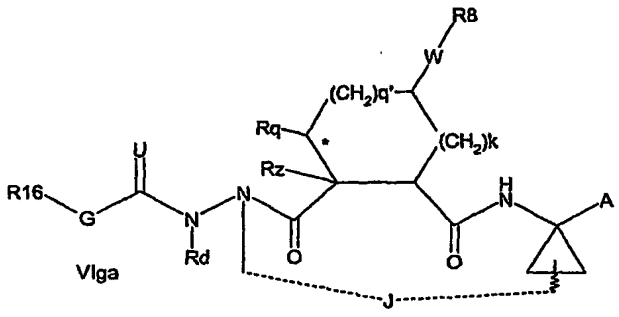


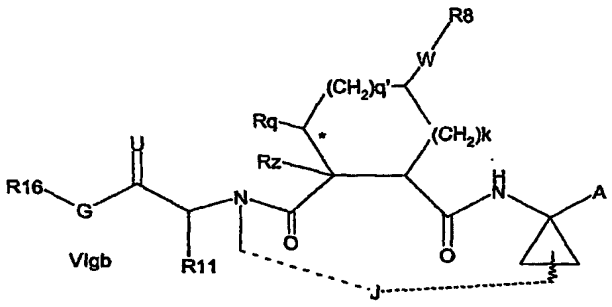

Igf

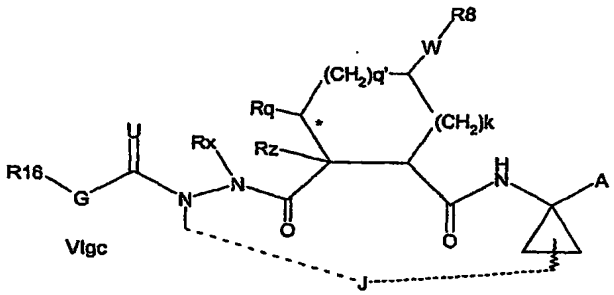
Favoured macrocyclic structures within Formula I, comprising both a P3 and P4 function, ie wherein m and n are each 1, include those of the formulae Iha-Ihd below.



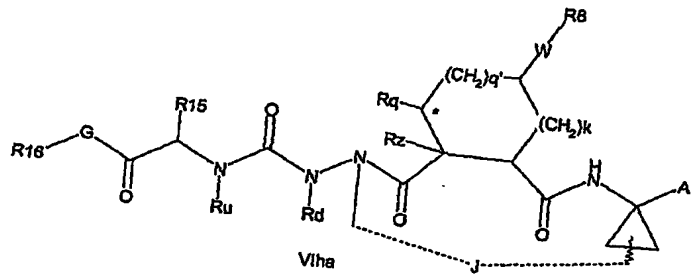

Favoured embodiments of macrocyclic structures within formula VI comprising a P3 function, but no P4 include those of the formula VIga- VIgc below:



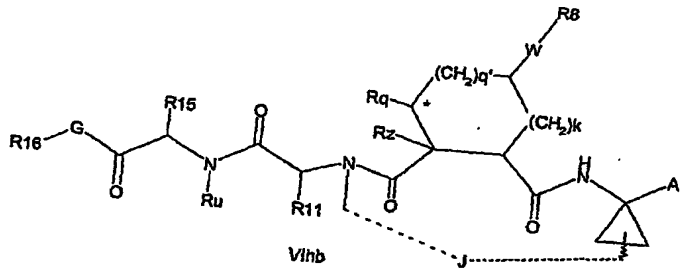



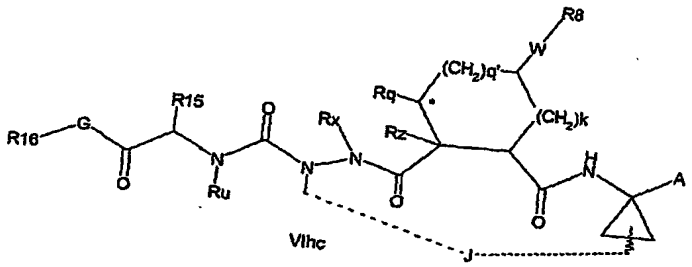

Favoured embodiments of macrocyclic structures within formula VI comprising both a P3 and P4 functions, include those of the formula VIha- VIhc below:




VIha




VIhb




VIhc

In general, in the optionally macrocyclic structures such as those illustrated above, linker J is a 3 to 10 chain atom, preferably 5 to 8 chain atom, such as 6 or 7 chain atom, saturated or unsaturated alkylene chain. The length of the chain will, of course, depend on whether J extends from Rd, Rj, Rx, Ry or $R^{11}$. Suitable chains are described in detail in WO 00/59929.

Conveniently, the J chain contains one or two heteroatoms selected from: O, S, NH, $NC_1$-$C_6$ alkyl or N-C(=O)$C_1$-$C_6$alkyl. More preferably, the J chain optionally contains one heteroatom selected from: NH, or N-C(=O)$C_1$-$C_6$alkyl, most preferably N(Ac). Most preferably, the chain containing a nitrogen atom is saturated. Alternatively, J

contains one heteroatom selected from: 0, or S. Preferably, this chain is substituted with $R^{14}$, such H or methyl. Even more preferably, J is saturated.

Alternatively, J contains a double bond, typically spaced one carbon from the cycloalkyl $R^7$ function. The double bond may be cis or trans.

Representative examples of J thus include pentanyl, hexanyl, heptanyl, any of which are substituted with $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ alkoxy, hydroxyl, halo, amino, oxo, thio or $C_1$-$C_6$ thioalkyl; penten:3:yl, hexen:4:yl, hepten:5 yl, where 3, 4 or 5 refers to a double bond between 3 carbon atoms 3 and 4, 4 and 5 etc.

Convenient $R^7$ and $R^{7'}$ groups include those wherein $R^{7'}$ is H and $R^7$ is *n*-ethyl, n-propyl, cyclopropylmethyl, cyclobutylmethyl, 2,2-difluoroethyl, or mercaptomethyl. Preferred embodiments include those wherein $R^7$ is n-propyl or 2,2-difluoroethyl.

Alternatively, $R^7$ and $R^{7'}$ together define a spiro-cycloalkyl function, such as a spiro-cyclobutyl ring, and more preferably a spiro-cyclopropyl ring. The ring is substituted or unsubstituted. Preferred substituents include mono or di-substitutions with $R^{7'a}$ wherein $R^{7'a}$ is $C_1$-$C_6$ alkyl, $C_3$-$C_5$cycloalkyl, or $C_2$-$C_6$ alkenyl, any of which is optionally substituted with halo. Alternatively the substituent may be a J linker as described above.

Particularly preferred substituents include $R^{7'a}$ as ethyl, vinyl, cyclopropyl, 1- or 2-bromoethyl, 1-or 2-fluoroethyl, 2-bromovinyl or 2-fluorethyl. Currently preferred stereochemistries for a spiro-cyclopropyl ring are defined below.

A favoured configuration for A is $-CR^4R^{4'}$ as illustrated in detail in PCT/EP03/10595, the contents of which are incorporated by reference.

Convenient $R^{4'}$ groups thus include $C_1$-$C_6$alkyl, such as methyl, ethyl, propyl, ethenyl and $-CHCHCH_3$. Alternative preferred $R^{4'}$ groups include aryl or heteroaryl such as optionally substituted phenyl, pyridyl, thiazolyl or benzimidazolyl or $C_1$-$C_3$alkylaryl or

$C_1$-$C_3$alkylheteroaryl, where the alkyl moiety is methyl, ethyl, propyl, ethenyl and –CHCHCH$_3$. Preferred aryl moieties include optionally substituted phenyl, benzothiazole and benzimidazole.

Favoured $R^4$ groups include -$NH_2$, fluoro or chloro. Alternative preferred $R^4$ groups include –OH and especially =O.

An alternative favoured configuration for A is CONHR$^3$, where $R^3$ is optionally substituted $C_0$-$C_3$alkylaryl, $C_0$-$C_3$alkylhetroaryl, O$C_0$-$C_3$alkylaryl or O$C_0$-$C_3$alkylhetroaryl. Appropriate susbstituents appear in the definitions section below.

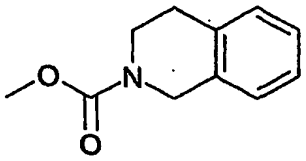
An alternative favoured configuration for A is CONHSO$_2$R$^2$, especially where $R^2$ is optionally substituted $C_1$-$C_6$ alkyl, preferably methyl, or optionally substituted $C_3$-$C_7$cycloalkyl, preferably cyclopropyl, or optionally substituted $C_0$-$C_6$alkylaryl, preferably optionally substituted phenyl. Appropriate susbstituents appear in the definitions section below.

A particularly preferred configuration for A is COOR$^1$, especially where $R^1$ is $C_1$-$C_6$ alkyl, such as methyl, ethyl, or tert-butyl and most preferably hydrogen.

Substituent -W-R8 on the cyclic P2 group can employ any of the proline substituents which are extensively described in WO 00/59929, WO 00/09543, WO 00/09558, WO 99/07734, WO 99/07733, WO 02/60926, WO 03/53349, WO03064416, WO03064455, WO03064456, WO0 03/99274, WO03/99316 and the like,

Preferred W functions include W is -OC(=O)NH-, -OC(=O)-, -NH-, -NR$^{8'}$-, -NHS(O)$_2$- or -NHC(=O)-, especially –OC(=O)NH- or –NH-. Favoured $R^8$ groups for such W functions include optionally substituted $C_0$-$C_3$-alkylcarbocyclyl or $C_0$-$C_3$-alkylheterocyclyl, including those described in WO0009543, WO0009558 and WO 00/174768. For example ester substituents, -W-$R^8$, on the cyclic P2 group, include those disclosed in WO 01/74768 such as $C_1$-$C_6$ alkyloxycarbonyl, $C_0$-

$C_3$aryloxycarbonyl, particularly (optionally substituted) phenyloxycarbonyll or $C_0$-$C_3$heterocyclyloxycarbonyl, especially



This publication also describes alternative –W-$R^8$ possibiliteis such as $C_1$-$C_6$ alkyl, such as ethyl, isopropyl, $C_0$-$C_3$-cycloalkyl such as cyclohexyl, 2,2-difluoroethyl, -C(=O)NRc, where Rc is $C_1$-$C_6$ alkyl, $C_0$-$C_3$-cyclopropyl, $C_0$-$C_3$-aryl or $C_0$-$C_3$-heterocyclyl.

Currently preferred W functions include –S- and especially –O-. Convenient values for $R^8$ in such embodiments include $C_0$-$C_3$alkylaryl, or $C_o$-$C_3$alkylhetroaryl either of which is optionally mono, di, or tri substituted with $R^9$, wherein;

$R^9$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$alkoxy, $NO_2$, OH, halo, trifluoromethyl, amino or amido optionally mono- or di-substituted with $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylaryl, $C_o$-$C_3$alkylhetroaryl, carboxyl, aryl or heteroaryl being optionally substituted with $R^{10}$; wherein

$R^{10}$ is $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_6$alkoxy, amino optionally mono- or di-substituted with $C_1$-$C_6$alkyl, $C_1$-$C_3$ alkyl amide), sulfonyl$C_1$-$C_3$alkyl, $NO_2$, OH, halo, trifluoromethyl, carboxyl, or hetroaryl.

Preferred $R^9$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$alkoxy, amino, di-($C_1$-$C_3$ alkyl)amino, $C_1$-$C_3$alkylamide, aryl or hetroaryl, the aryl or hetroaryl being optionally substituted with $R^{10}$; wherein

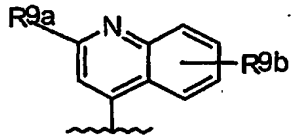
$R^{10}$ is $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_6$alkoxy, amino, mono- or di-$C_1$-$C_3$ alkylamino, amido, $C_1$-$C_3$ alkylamide, halo, trifluoromethyl, or hetroaryl.

Preferred $R^{10}$ include $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, amino optionally mono- or di substituted with $C_1$-$C_3$ alkyl, amido, $C_1$-$C_3$-alkylamide, halo, or hetroaryl.

Particularly preferred $R^{10}$ include methyl, ethyl, isopropyl, tert-butyl, methoxy, chloro, amino optionally mono- or di substituted with $C_1$-$C_3$ alkyl, amido, $C_1$-$C_3$alkylamide, or $C_1$-$C_3$alkyl thiazole.

Especially preferred $R^8$ include 1-naphthlmethyl, 2-naphtylmethyl, benzyl, 1-naphthyl, 2-naphthyl, or quinolinyl unsubstituted , mono, or disubstituted with $R^9$ as defined, in particular 1-naphthylmethyl, or quinolinyl unsubstituted , mono, or disubstituted with $R^9$ as defined.

A currently preferred $R^8$ is:

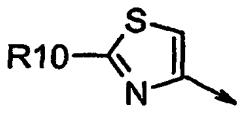


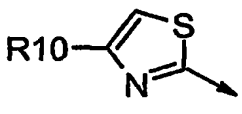

wherein $R^{9a}$ is $C_1$-$C_6$ alkyl; $C_1$-$C_6$alkoxy; thio$C_1$-$C_3$alkyl; amino optionally substituted with $C_1$-$C_6$alkyl; $C_0$-$C_3$alkylaryl; or $C_0$-$C_3$ alkylheteroaryl, $C_0$-$C_3$ alkylheterocyclyl, said aryl, heteroaryl or heterocycle being optionally substituted with $R^{10}$ wherein

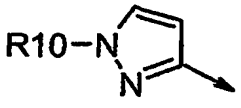
$R^{10}$ is $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_6$alkoxy, amino optionally mono- or di-substituted with $C_1$-$C_6$alkyl, amido, $C_1$-$C_3$alkyl amide, heteroaryl or heterocyclyl; and

$R^{9b}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$-alkoxy, amino, di($C_1$-$C_3$alkyl)amino, ($C_1$-$C_3$alkyl) amide, $NO_2$, OH, halo, trifluoromethyl, carboxyl.

Convenient $R^{9a}$ include aryl or heteroaryl, all optionally substituted with $R^{10}$ as defined, especially where $R^{9a}$ is selected from the group consisted of:

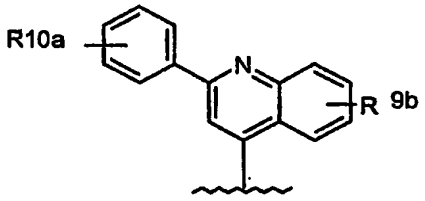


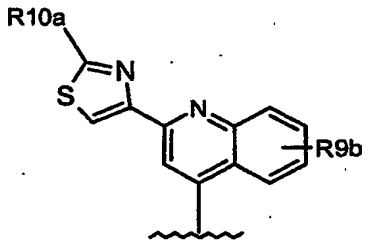
wherein $R^{10}$ is H, $C_1$-$C_6$alkyl, or $C_0$-$C_3$alkyl-$C_3$-$C_6$cycloalkyl, amino optionally mono- or di-substituted with $C_1$-$C_6$alkyl, amido, ($C_1$-$C_3$alkyl)amide, heteroaryl or heterocyclyl.

$R^{9a}$ is conveniently phenyl and thus $R^8$ is:




wherein $R^{10a}$ is H, $C_1$-$C_6$alkyl; $C_1$-$C_6$alkoxy; or halo; and $R^{9b}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$-alkoxy, amino, di($C_1$-$C_3$alkyl)amino, ($C_1$-$C_3$alkyl)amide, $NO_2$, OH, halo, trifluoromethyl, carboxyl.

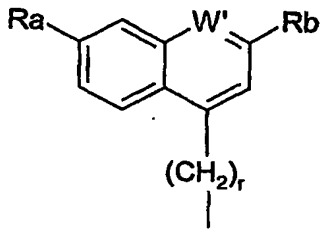
An alternative preferred $R^8$ is:




wherein $R^{10a}$ is H, $C_1$-$C_6$alkyl, or $C_0$-$C_3$alkyl-$C_3$-$C_6$cycloalkyl, amino optionally mono- or di-substituted with $C_1$-$C_6$alkyl, amido, ($C_1$-$C_3$ alkyl)amide, heteroaryl or heterocyclyl; and $R^{9b}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$-alkoxy, amino, di($C_1$-$C_3$ alkyl)amino, ($C_1$-$C_3$ alkyl)amide, $NO_2$, OH, halo, trifluoromethyl, or carboxyl.

In the immediately above described embodiments $R^{9b}$ is conveniently $C_1$-$C_6$-alkoxy, preferably methoxy.

A further ether substituent $R^8$ has the formula

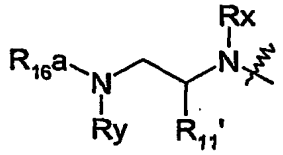



where W' is N or CH, r is 0 or 1, Ra is H, $C_1$-$C_6$ alkyl, $C_0$-$C_3$cycloalkyl, $C_1$-$C_6$ alkyloxy, hydroxy or amine and Rb is H, halo, $C_1$-$C_6$ alkyl, $C_0$-$C_3$cycloalkyl, $C_1$-$C_6$ alkyloxy, $C_1$-$C_6$ thioalkyl, cycloalkyl$C_0$-$C_3$alkyloxy, $C_1$-$C_3$alkyloxy$C_1$-$C_3$alkyl, $C_0$-$C_3$aryl or $C_0$-$C_3$heterocyclyl. A particularly preferred ether substituent is 7-methoxy-2-phenyl-quinolin-4-yl oxy.

Preferred P3 groups resemble natural or unnatural amino acids, especially aliphatic amino acids, such as L-valyl, L-leucyl, L- isoleucyl or L- t-leucyl. Further preferred P3 groups, as shown in WO 02/01898 include $C_0$-$C_3$ cycloalkyl, especially cyclohexylalanine, optionally substituted with $CO_2Rg$, where Rg is H, is $C_1$-C6 alkyl, $C_0$-$C_3$-alkylaryl, $C_0$-$C_3$alkylhet, $C_0$-$C_3$alkylcycloalkyl or amine; or N-acetylpiperidine or tetrahydropyran. Preferred $R^{11}$ groups thus include $C_1$-$C_6$alkyl, $C_0$-$C_3$ alkyl$C_3$-$C_7$ cycloalkylyl, $C_0$-$C_3$alkylaryl or $C_0$-$C_3$ alkylheteroaryl, any of which is optionally substituted with hydroxy, halo, amino, $C_1$-$C_6$alkoxy, $C_1$-$C_6$thioalkyl, $COOR^{14}$, carboxyl, ($C_1$-$C_6$alkoxy)carbonyl, aryl, heteroaryl or heterocyclyl, especially where the substituent is hydroxy or $COOR^{14}$.

Particularly preferred $R^{11}$ include tert-butyl, iso-butyl, cyclohexyl, phenylethyl, 2,2-dimethyl-propyl, cyclohexylmethyl, phenylmethyl, 2-pyridylmethyl, 4-hydroxy-phenylmethyl, or carboxylpropyl. The most preferred $R^{11}$ values are currently tert-butyl, iso-butyl, or cyclohexyl.

Favoured embodiments of the invention include those wherein P4 is absent (ie n is 0) and wherein the P3 function lacks a carbonyl, ie U is absent. Currently preferred substructures include those of formula Ii below:



Ii

wherein

Rx and Ry are as defined above, preferably H,

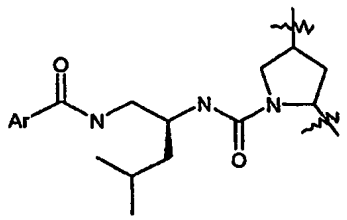
$R^{11'}$ is $C_1$-$C_6$ alkyl, preferably $C_3$-$C_5$ branched alkyl such as the side chains of L-valyl, L-leucyl, L-isoleucyl, L-t-leucyl; or $C_0$-$C_2$alkyl$C_3$-$C_7$ cycloalkyl such as cyclohexyl or cyclohexylmethyl;

$R^{16a}$ is –Rba, -S(=O)pRba, -(=O)Rba

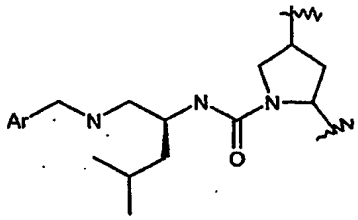
Rba is $C_1$-$C_6$ alkyl, $C_0$-$C_3$-alkylheterocyclyl, $C_0$-$C_3$-alkylcarbocyclyl.

Alternatively, compounds of partial structure Ii may be macrocyclised between an appropriate value of $R^7$ and one of Rx, Ry or $R^{11'}$.

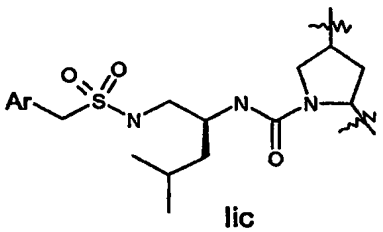
Representative embodiments of P3 groups which lack a carboxy function (ie variable U is absent) include those of formula Iia-Iid below:



IIa



IIb



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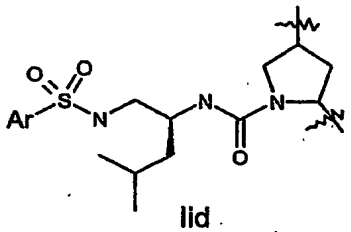


IId

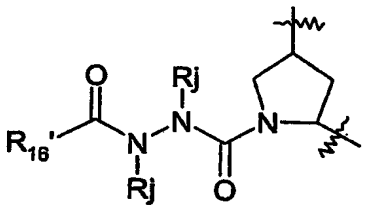
where Ar is carbocyclyl or heterocyclyl, especially aryl or heteroaryl, any of which is optionally substituted with $R^9$. Although the partial structures of Formulae IIa - IId have been illustrated in the context of a compound within Formula I, it will be apparent that such configurations of Formula II apply also to Formula VI, and to other values of q,q' and k. Similarly, although the partial structures of formulae IIc and IId show an R11 group corresponding to leucine, it will be apparent that these configurations will be applicable to other R11 groups, especially those resembling the side chains of natural or unnatural L-amino acids, for example t-butyl alanine/t-leucine.

$R^{15}$ in those compounds of the invention wherein n is 1, is preferably optionally substituted $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl or $C_0$-$C_3$alkyl$C_3$-$C_7$cycloalkyl, any of which may be optionally substituted. Preferred P4 groups are typically analogues of natural or unnatural amino acids, especially aliphatic amino acids such as L-valyl, L-leucyl, L-isoleucyl , L-t-leucyl or L-cyclohexylalanine and thus favoured $R^{15}$ groups include cyclohexyl, cyclohexylmethyl, tert-butyl, iso-propyl, or iso-butyl.

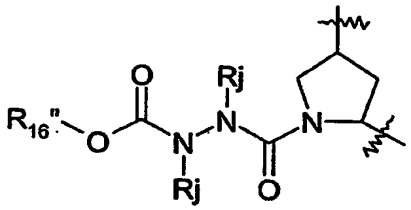
Preferred G values include –NRy-, especially wherein Ry is methyl or preferably H, or hydrazine.

A further preferred G value is O thereby defining an ester with the carbonyl of P4 (if present) or the carbonyl of P3 (if present) or an ether in the case of variants wherein group U is absent. Conventional pharmaceutically acceptable ethers or esters capping groups for $R^{16}$ include $C_1$-$C_6$alkyl (especially methyl or t-butyl), $C_0$-$C_3$alkylheterocyclyl (especially pyridyl, benzimidazolyl, piperidyl, morpholinyl, piperazinyl) or $C_0$-$C_3$alkylcarbocyclyl (especially phenyl, benzyl, indanyl) any of which is optionally substituted with hydroxy, halo, amino, or $C_1$-$C_6$alkoxy.

Favoured compounds of the invention can comprise a hydrazine functionality, for example where X is –NHNH- and m is 1; with n being zero or 1. Alternatively, especially where m is zero, G can be –NHNH-. Compounds will generally not comprise a hydrazine at both G and X. Typical hydrazines within Formula I, wherein m and n are zero include compounds of the partial structures Ija- Ijb below:



Ija

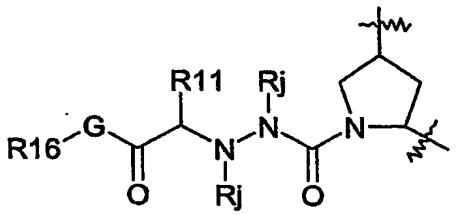


Ijb

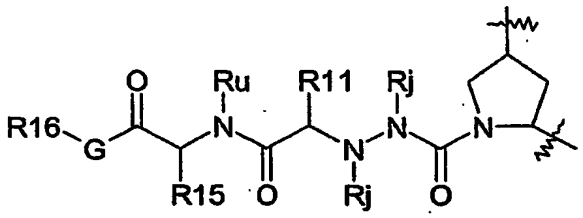
$R^{16}$ in formulae Ija and Ijb can be regarded as an alkyl (or $C_1$-$C_3$-alkylheterocyclyl or $C_1$-$C_3$alkyl carbocyclyl) wherein the first alkyl carbon is substituted with an oxo group to define the keto function and $R^{16'}$ is the remainder of the alkyl, alkylheterocyclyl or alkylcarbocyclyl moiety. Formula Ijb depicts a variant where $R^{16}$ is a methylene group whose carbon is substituted with an oxo substituent and also –ORb, where Rb is as defined above, typically, $C_1$-$C_6$ alkyl, such as t-butyl, $C_0$-$C_3$ alkylheterocyclyl such as pyridyl, or $C_0$-$C_3$-carbocyclyl, such as benzyl or phenyl, any of which is optionally substituted as defined above. Compounds of partial structures Ija and Ijb can be

linear molecules as shown (both Rj are H), or preferably one of the depicted Rj groups can be macrocyclised via J to an appropriate $R^7$ group.

Alternative hydrazines of Formula I where m is 1 include those of partial structures Ijc and Ijd below:




Ijc

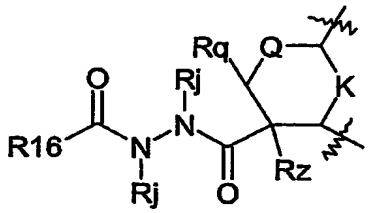



Ijd

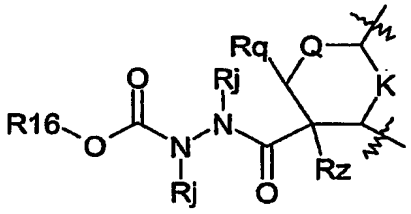
where $R^{16}$, G, $R^{11}$ Rj and Ru are as defined for formula I above. Compounds of partial structures Ijc and Ijd can be linear molecules as shown (both Rj are H), or preferably one of the depicted Rj groups, or the R11 group can be macrocyclised via J to an appropriate $R^7$ group

Although formula Ija-Ijd are depicted with a proline analogue as P2, it will be apparent that this aspect of the invention is equally adapted to other configurations of q and k.

Favoured embodiments within formula VI include those with the substructures of formula VIja- VIjb:




VIja

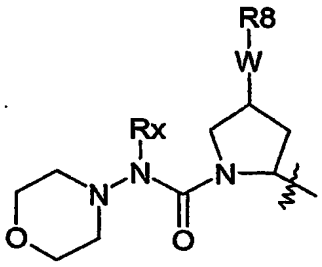



VIjb

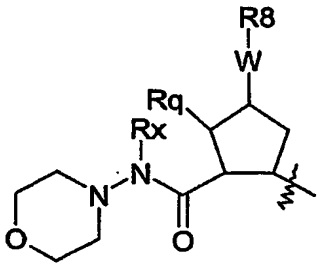
where Rq and Rz are as defined above and Q and K are $-(CH_2)_{q'}$ and $-(CH_2)_k$ respectively. Currently preferred embodiments within Formulae VIja and VIjb include thoses wherein q' is zero (i.e. Q is a bond) and k is 1, i.e. K is methylene, especially

those wherein Rq is H or methyl and Rz is H or forms an olefinic bond. Compounds of partial structures VIja and VIjb can be linear molecules as shown (both Rj are H), or preferably one of the depicted J groups can be macrocyclised to an appropriate $R^7$ group

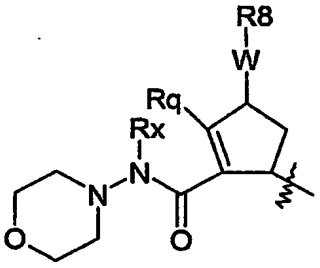
Alternative hydrazine-like configuration are found when G is amino, and m and n are 0, and $R^{16}$ is an N-linked unsaturated heterocycle as defined below, for example pyridyl or pyrimidyl or a saturated heterocycle as defined below, such as piperazinyl, piperidinyl and especially morpholinyl., Examples of such embodiments include those of the formulae Ije and VIjc and VIjd:




Ije




VIjc




VIjd

Compounds of partial structures Ije, VIjc and VIjd can be linear molecules as shown or preferably Rx can be macrocyclised via J to an appropriate $R^7$ group. Although these partial structures are depicted with a five membered ring for P2 , it will be readily apparent that this configuration extends to other values of q, q' and k. Similarly these configurations will be applicable to other N-linked heterocycles as $R^{16}$.

Returning now to Formulae I and VI in general, favoured $R^{16}$ groups for the compounds of the invention include 2-indanol, indanyl, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, cyclohexylmethyl, 2,3-methylenedioxybenzyl, cyclohexyl, phenyl, benzyl, 2-pyridylmethyl, cyclobutyl, iso-butyl, n-propyl, methyl, or 4-methoxyphenylethyl.

Currently preferred $R^{16}$ groups include 2-indanol, indan, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, 2,3-methylenedioxybenzyl, or cyclohexylmethyl.

Unnatural amino acids include L-amino acids wherein the side chain is not one of the 20 naturally occurring amino acids. Examples of non-natural amino acids include L-beta-methylsulfonylmethylalanine, L-cyclohexylalanine, L-tertiary-leucine, L-norleucine, L-norvaline, L-ornithine, L-sarcosine, L-citurline, L-homophenylalanine, L-homoserine, L-beta-(1-napthyl)alanine, L-beta-(2-napthyl)alanine etc. Non natural amino acids also include the D-amino acids corresponding to the 20 natural amino acids and D-amino acids bearing other side chains, such as those listed above.

'$C_1$-$C_6$-alkyl' (also abbreviated as $C_1$-$C_6$-alk in compound expressions such as $C_1$-$C_6$-alkyloxy etc) as applied herein is meant to include straight and branched chain aliphatic carbon chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, heptyl and any simple isomers thereof. The alkyl group may have an unsaturated bond. Additionally, any C atom in $C_1$-$C_6$-alkyl may optionally be substituted by one, two or where valency permits three halogens and/or a heteroatom S, O, NH. If the heteroatom is located at a chain terminus then it is appropriately substituted with one or 2 hydrogen atoms. $C_1$-$C_4$alkyl and $C_1$-$C_5$alkyl have the corresponding meaning to $C_1$-$C_6$alkyl adjusted as necessary for the carbon number.

'$C_1$-$C_3$-alkyl' as applied herein includes methyl, ethyl, propyl, isopropyl, cyclopropyl, any of which may be optionally substituted as described in the paragraph above or in the case of $C_2$ or $C_3$, bear an unsaturated bond such as $CH_2$=CH.

'Amine' includes $NH_2$, $NHC_1$-$C_3$-alkyl or $N(C_1$-$C_3$-alkyl$)_2$.

'Halo' or halogen as applied herein is meant to include F, Cl, Br, I, particularly chloro and preferably fluoro.

'$C_0$-$C_3$-aryl' as applied herein is meant to include a phenyl, naphthyl or phenyl fused to $C_3$-$C_7$ cyclopropyl such as indanyl, which aryl is directly bonded (ie $C_0$) or through an intermediate methyl, ethyl, propyl, or isopropyl group as defined for $C_0$-$C_3$-alkyl above. Unless otherwise indicated the aryl and/or its fused cycloalkyl moiety is substituted with 1-3 substituents selected from halo, hydroxy, nitro, cyano, carboxy, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy-$C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, amino, azido, oxo, mercapto, nitro $C_0$-$C_3$carbocyclyl, $C_0$-$C_3$-heterocyclyl. "Aryl" has the corresponding meaning.

'$C_0$-$C_3$-carbocyclyl' as applied herein is meant to include $C_0$-$C_3$-aryl and $C_o$-$C_3$ alkyl $C_3$-$C_7$ cycloalkyl. Unless otherwise indicated the aryl or cycloalkyl group is optionally substituted with 1-3 substituents selected from halo, hydroxy, nitro, cyano, carboxy, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy-$C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, amino, azido, oxo, mercapto, nitro, $C_0$-$C_3$carbocyclyl and/or $C_0$-$C_3$-heterocyclyl. "Carbocyclyl" has the corresponding meaning, i.e. where the $C_0$-$C_3$ alkyl linkage is absent

'$C_0$-$C_3$-heterocycylyl' as applied herein is meant to include a monocyclic, saturated or unsaturated, heteroatom-containing ring such as piperidinyl, morpholinyl, piperazinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazinolyl, isothiazinolyl, thiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, furanyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, pyrazolyl, or any of such groups fused to a phenyl ring, such as quinolinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazinolyl, benzisothiazinolyl, benzothiazolyl, benzoxadiazolyl, benzo-1,2,3-triazolyl, benzo-1,2,4-triazolyl, benzotetrazolyl, benzofuranyl, benzothienyl, benzopyridyl, benzopyrimidyl, benzopyridazinyl, benzopyrazolyl etc, which ring is bonded directly ie ($C_0$),or through an intermediate methyl, ethyl, propyl, or isopropyl group as defined for $C_0$-$C_3$-alkyl above. Any such non-saturated rings having an aromatic character may be referred to as heteroaryl herein. Unless otherwise indicated the hetero ring and/or its fused phenyl moeity is optionally substituted with 1-3 substituents selected from halo, hydroxy, nitro, cyano, carboxy, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkoxy-$C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkanoyl, amino, azido, oxo, mercapto, nitro, $C_0$-$C_3$ carbocyclyl, $C_0$-$C_3$-

heterocyclyl. "Heterocyclyl" and "Heteroaryl" has the corresponding meaning, i.e. where the $C_0$-$C_3$ alkyl linkage is absent.

Typically heterocycyl and carbocyclyl groups are thus a monocyclic ring with 5 or especially 6 ring atoms, or a bicyclic ring structure comprising a 6 membered ring fused to a 4, 5 or 6 membered ring.

Typical such groups include $C_{3-8}$ cycloalkyl, phenyl, benzyl, tetrahydronaphthyl, indenyl, indanyl, heterocyclyl such as from azepanyl, azocanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiopyranyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, tetrahydroquinazolinyl and quinoxalinyl, any of which may be optionally substituted as defined herein.

The saturated heterocycle thus includes radicals such as pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl, indolinyl, azetidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, hexahydropyrimidinyl, hexahydropyridazinyl, 1,4,5,6-tetrahydropyrimidinylamine, dihydro-oxazolyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1 -dioxide and imidazolidinyl-2,4-dione, whereas the unsaturated heterocycle include radicals with an aromatic character such as furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl. In each case the heterocycle may be condensed with a phenyl ring to form a bicyclic ring system.

In general preferred monocyclic rings include substituted pyridyl, substituted pyrimidyl, substituted phenyl, particularly phenyl substituted with a cyclic group such as pyrrolidine-1-yl, piperidine-1-yl, morpholin-4-yl, 4-methylpiperazin-1-yl, 2-morpholin-4-yl-ethylamino, and piperazin-1-yl, piperid-4-yl or N-piperazinyl, N-substituted with Ra or piperidin-1-yl which is 4-substituted with -NRaRb.

Synthesis of the compounds of the present invention can be performed by different chemical strategies in solution or solid phase or a combination of both. The suitably protected individual building blocks can first be prepared and subsequently coupled together i.e. P2+P1→ P2-P1. Alternatively, precursors of the building blocks can be coupled together and modified at a later stage of the synthesis of the inhibitor sequence. Further building blocks, precursors of building blocks or prefabricated bigger fragments of the desired structure, can then be coupled to the growing chain, e.g. $R^{16}$-G-P3+ E-P2-P1→ $R^{16}$-G-P3-P2-P1 or $R^{16}$-G-P4-P3+E-P2-P1→ $R^{16}$-G-P4-P3-E-P2-P1.

Coupling between two amino acids, an amino acid and a peptide, or two peptide fragments can be carried out using standard coupling procedures such as the azide method, mixed carbonic-carboxylic acid anhydride (isobutyl chloroformate) method, carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimide) method, active ester (pnitrophenyl ester, N-hydroxysuccinic imido ester) method, Woodward reagent K-method, carbonyldiimidazole method, phosphorus reagents or oxidation-reduction methods. Some of these methods (especially the carbodiimide method) can be enhanced by adding 1-hydroxybenzotriazole or 4-DMAP. These coupling reactions can be performed in either solution (liquid phase) or solid phase.

More explicitly, the coupling step involves the dehydrative coupling of a free carboxyl of one reactant with the free amino group of the other reactant in the present of a coupling agent to form a linking amide bond. Descriptions of such coupling agents are found in general textbooks on peptide chemistry, for example, M. Bodanszky,

"Peptide Chemistry", 2nd rev ed., Springer-Verlag, Berlin, Germany, (1993) hereafter simply referred to as Bodanszky, the contents of which are hereby incorporated by reference. Examples of suitable coupling agents are N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole in the presence of N,N'- dicyclohexylcarbodiimide or N-ethyl-N'- [ (3dimethylamino) propyl] carbodiimide. A practical and useful coupling agent is the commercially available (benzotriazol-1-yloxy) tris- (dimethylamino) phosphonium hexafluorophosphate, either by itself or in the present of 1-hydroxybenzotriazole or 4-DMAP. Another practical and useful coupling agent is commercially available 2-(IH-benzotriazol-1-yl)-N, N, N',N'- tetramethyluronium tetrafluoroborate. Still another practical and useful coupling agent is commercially available 0-(7-azabenzotrizol-1-yl)-N, N,N', N'-tetramethyluronium hexafluorophosphate.

The coupling reaction is conducted in an inert solvent, e. g. dichloromethane, acetonitrile or dimethylformamide. An excess of a tertiary amine, e. g. diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine or 4-DMAP is added to maintain the reaction mixture at a pH of about 8. The reaction temperature usually ranges between 0 °C and 50 °C and the reaction time usually ranges between 15 min and 24 h.

The functional groups of the constituent amino acids generally must be protected during the coupling reactions to avoid formation of undesired bonds. The protecting groups that can be used are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), hereafter referred to simply as Greene, the disclosures of which are hereby incorporated by reference.

The α-carboxyl group of the C-terminal residue is usually protected as an ester that can be cleaved to give the carboxylic acid. Protecting groups that can be used include 1) alkyl esters such as methyl, trimethylsilyl and t.butyl, 2) aralkyl esters such as benzyl and substituted benzyl, or 3) esters that can be cleaved by mild base or mild reductive means such as trichloroethyl and phenacyl esters.

The α-amino group of each amino acid to be coupled must be protected. Any protecting group known in the art can be used. Examples of such groups include: 1) acyl groups such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate groups such as benzyloxycarbonyl (Cbz or Z) and substituted bensyloxycarbonyls, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate groups such as tertbutyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate groups such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl groups such as triphenylmethyl and benzyl; 6) trialkylsilyl such as trimethylsilyl; and 7) thiol containing groups such asphenylthiocarbonyl anddithiasuccinoyl. The preferred α-amino protecting group is either Boc or Fmoc. Many amino acid derivatives suitably protected for peptide synthesis are commercially available.

The α-amino protecting group is cleaved prior to the next coupling step. When the Boc group is used, the methods of choice are trifluoroacetic acid, neat or in dichloromethane, or HCl in dioxane or in ethyl acetate. The resulting ammonium salt is then neutralized either prior to the coupling or in situ with basic solutions such as aqueous buffers, or tertiary amines in dichloromethane or acetonitrile or dimethylformamide. When the Fmoc group is used, the reagents of choice are piperidine or substituted piperidine in dimethylformamide, but any secondary amine can be used. The deprotection is carried out at a temperature between 0 °C and room temperature usually 20-22 °C.

Any of the natural or non-natural amino acids having side chain functionalities will typically be protected during the preparation of the peptide using any of the above described groups. Those skilled in the art will appreciate that the selection and use of appropriate protecting groups for these side chain functionalities depend upon the amino acid and presence of other protecting groups in the peptide. In the selection of such protecting groups it is desirable that the group is not removed during the deprotection and coupling of the α-amino group.

For example, when Boc is used as the α-amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chain of amino acids such as Lys and Arg; acetamidomethyl, benzyl (Bn), or tert-butylsulfonyl moities can be used to protect the sulfide containing side chain of cysteine; benzyl (Bn) ethers can be used to protect the hydroxy containing side chains of serine, threonine or hydroxyproline; and benzyl esters can be used to protect the carboxy containing side chains of aspartic acid and glutamic acid.

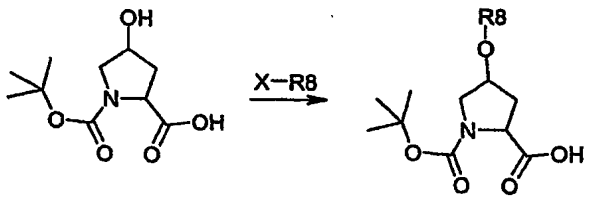
When Fmoc is chosen for the α-amine protection, usually tert. butyl based protecting groups are acceptable. For instance, Boc can be used for lysine and arginine, tert.butyl ether for serine, threonine and hydroxyproline, and tert-butyl ester for aspartic acid and glutamic acid. Triphenylmethyl (Trityl) moiety can be used to protect the sulfide containing side chain of cysteine.

Once the inhibitor sequence is completed any protecting groups are removed in whatever manner is dictated by the choice of protecting groups. These procedures are well known to those skilled in the art.

In compounds of Formula I, the P2 unit comprises a nitrogen-containing ring residue which is substituted with the W and R8 moieties.

Synthesis of heterocyclic P2 building blocks

Compounds wherein W is O and R8 is alkyl, $C_0$-$C_3$ carbocycylyl, $C_0$-$C_3$-heterocycylyl can be prepared according to the procedure described by E. M. Smith et al. (J. Med. Chem. (1988), 31, 875-885), as depicted in Scheme 1, which illustrates the technique in a moiety wherein q and k are 1.

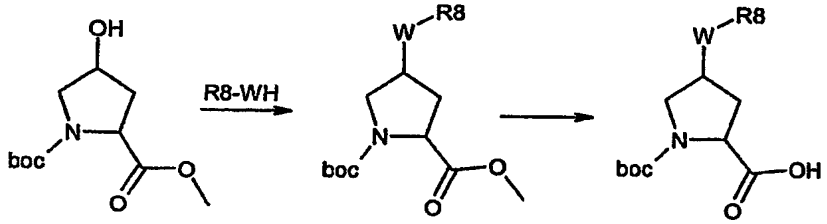



1a 1b

Scheme 1

Commercially available Boc-4-(R)-hydroxyproline, or any suitable hydroxy substituted proline analogue, such as an hydroxypiperidoic acid is treated with a base such as sodium hydride or potassium t.butoxide in a solvent like dimethylformamide and the resulting alkoxide is reacted with an alkylating agent, $R^8$-X, wherein X is a suitable leaving group such as a halide like chloride, bromide or iodide, providing the desired substituted proline derivative.

Alternatively, when W is O or S and $R^8$ is carbocyclyl such as phenyl or heterocyclylyl such as heteroaryl, the P2 building blocks can also be prepared via a Mitsunobu reaction (Mitsunobu, 1981, Synthesis, January, 1-28; Rano et al., Tetrahedron Lett., 1995, 36, 22, 3779-3792; Krchnak et al., Tetrahedron Lett., 1995, 36, 5, 6193-6196; Richter et al., Tetrahedron Lett., 1994, 35, 27, 4705-4706) as shown in Scheme 2, which illustrates the technique in a moiety wherein q and k are 1 .



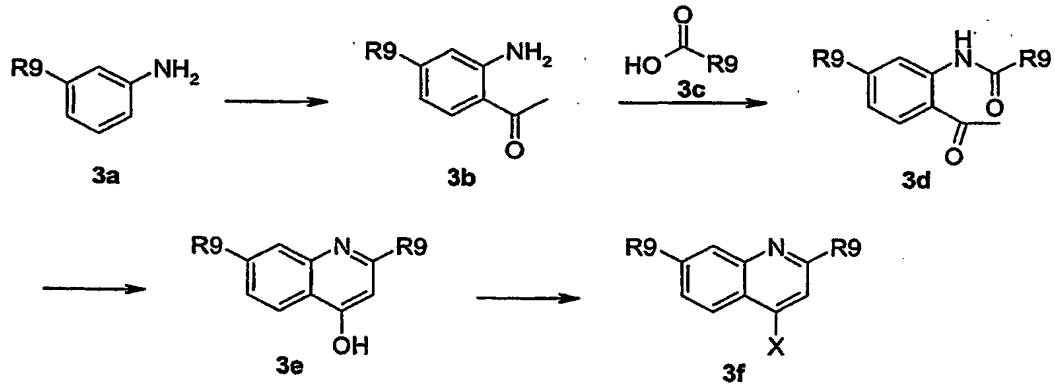

2a 2b 2c

Scheme 2

Treatment of the appropriate hydroxy substituted proline analogue, such as a hydroxypiperidoic acid, here shown as commercially available Boc-4-hydroxyproline methyl ester, with the desired alcohol or thiol ($R^8$-WH) in the presence of triphenylphosphine and an activating agent like diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD) or the like, provides the ester compound (2b). Hydrolysation of the ester to the acid by standard procedures provides the P2 building block (2c).

Alcohol (2a) can alternatively be treated with phosgene thus providing the corresponding chloroformate which upon reaction with an amine, $R^8NH_2$, in the presence of a base like sodium hydrogen carbonate or triethylamine, provides carbamates i.e. W is -OC(=O)NH-, whereas reaction of alcohol (2a) with an acylating agent, R8-CO-X, like an acid anhydride or acid halide for instance the acid chloride, to provide esters, i.e. W is -OC(=O)-.

Various alcohols $R^8$-OH, and alkylating agents $R^8$-X are described in WO 00/09543 and WO00/59929. An example of the synthesis wherein $R^8$ is a substituted quinoline derivative is shown in Scheme 3.

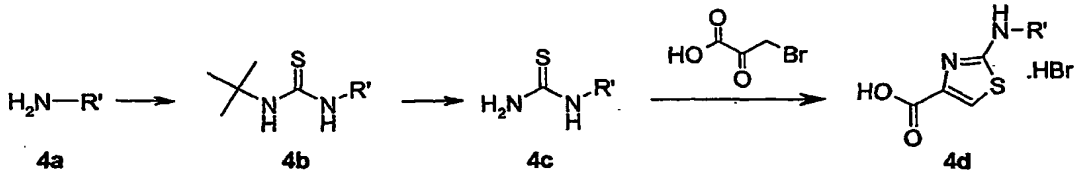



Scheme 3

Friedel-Craft acylation of a suitable substituted aniline (3a), available either commercially or in the literature, using an acylating agent like acetyl chloride or the

like in the presence of boron trichloride and aluminium trichloride in a solvent like dichloromethane provides (3b). Coupling of (3b) to a heterocyclic carboxylic acid (3c) under basic conditions, such as in pyridine, in the presence of an activating agent for the carboxylate group, for instance $POCl_3$, followed by ring closure and dehydration under basic conditions like potassium tert-butoxide in tert-butanol provides quinoline derivative (3e). Quinoline derivative (3e) can be coupled in a Mitsunobu reaction to an alcohol as described above, or the hydroxy group can be displaced by a suitable leaving group such as a halide like chloride, bromide or iodide, by treatment of quinoline (3e) with an appropriate halogenating agent for example phosphoryl chloride or the like.

A variety of carboxylic acids with the general structure (3c) can be used in Scheme 3. These acids are available either commercially or in the literature. An example of the preparation of 2-(substituted)-amino-carboxy-aminothiazole derivatives, following the procedure by Berdikhina et al. Chem. Heterocycl. Compd. (Engl. Transl.) (1991), 427-433, is shown below.



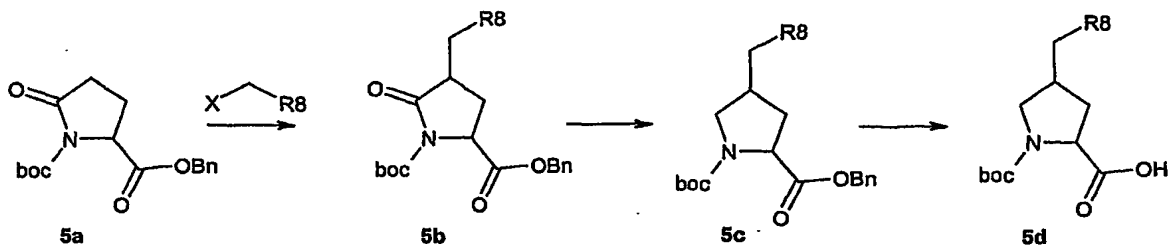

Scheme 4

Thiourea (4c) with different alkyl substituents R' can be formed by reaction of the appropriate amine (4a) with tert-butylisothiocyanate in the presence of a base like diisopropylethylamine in a solvent like dichloromethane followed by removal of the tert- butyl group under acidic conditions. Subsequent condensation of thiourea derivative (4c) with 3-bromopyruvic acid provides the acid (4d).

P2 building blocks wherein the $R^8$ substituent is attached via an amine, amide, urea or sulphonamide, can be prepared from aminoproline analogues achieved either

from a suitable commercially available aminoproline, etc derivative or by transforming the hydroxy group of the corresponding hydroxy derivative into an azide group for example by transforming the hydroxy group into a suitable leaving group such as a mesylate or halogen like chloride, followed by substitution of the leaving group with azide or by the use of an azide transfer agent like diphenylphosphoryl azide (DPPA). Reduction of the azide by catalytic hydrogenation or any other suitable reduction method provides the amine. The amino derivative can be reacted in a displacement reaction with an alkylating agent of the general formula $R^8$-X wherein $R^8$ and X are as described for scheme 1, to form P2 building blocks for use in the preparation of compounds of general formula I or VI, wherein W is –NH-. Reaction of the aminoproline analogue with an acid of the general formula $R^8$-COOH under standard amide coupling conditions provides compounds wherein the R8 substituent is linked via an amide bond, whereas reaction of the aminoproline analogue with an appropriate derivative of sulphonic acid, $R^8$-$S(O)_2$-X where X is a leaving group for example chloride, in the presence of a base, provides sulphonamides. Compounds wherein the linkage between the cyclic scaffold and the R8 substituent is constituted of a urea group can for example be achieved by treatment of amino proline analogue with phosgene to afford the corresponding chlorocarbamate followed by reaction with the desired amine. Alternatively, the amino proline analogue can be reacted with the carbamoyl chloride or isocyanate of the desired R8 substituent for the formation of the urea linkage. It will be apparent that corresponding reactions will be available for P2 groups with other ring sizes and substitution pattern.

4-Substituted heterocyclyl derivatives such as 4-substituted proline for use as P2 building blocks where W is -$CH_2$- can be prepared as shown in Scheme 5, which illustrates the technique on a moiety where q and k is 1, according to the procedures described by J. Ezquerra et al., Tetrahedron, 1993, 38, 8665-8678 and C. Pedregal et al. Tetrahedron Lett., 1994, 35, 2053-2056.




Scheme 5

Treatment of suitably acid protected pyrrolidone or piperidinone such as commercially available Boc-pyroglutamic acid (5a) with a strong base such as lithium diisopropylamide in a solvent like tetrahydrofuran followed by addition of an alkylating agent $R^8$-$CH_2$-X where X is a suitable leaving group such as a halide like chloride or bromide, followed by reduction of the amide and deprotection of the ester gives the desired compound (5d).

Compounds with alternative ring size and/or position of the W-$R^8$ substituent of the proline derivatives in scheme 1, 2 and 5 may also be used in the preparation of compounds according to the present invention. For example, alkylation of commercially available 3-hydroxyproline provides compounds of the general formula (I) wherein k is 0 and q is 2. Correspondingly, alkylation of 5-hydroxyproline, prepared for example as described by Hallberg et al., J. Med. Chem. (1999), 4524-4537, provides compounds of the general formula (I) wherein k is 2 and q is 0.

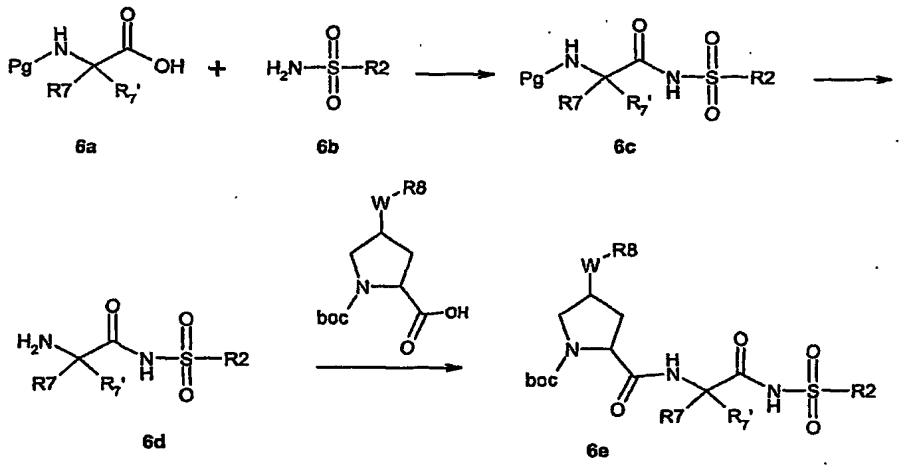
Various methods for the preparation of hydroxylated 2-piperidine carboxylic acids are described in the literature se for instance Celestini et al., Org. Lett., (2002), 1367-1370, Hoarau et al., Tetrahedron: Asymmetry, (1996), 2585-2594, Zhu et al., Tetrahedron Lett., 41, (2000), 7033-7036. For example, the corresponding pyridine carboxylic acids can be reduced to provide hydroxylated 2-piperidine carboxylic acids. Enzymatical methods can also be used for the preparation of hydroxylated proline analogues. For example, a 3-hydroxy substituent can be introduced on commercially available 4, 5, and 6 membered heterocyclic acids by the use of proline 3-hydroxylase as described by Ozaki et al., Tet. Letters, 40, (1999), 5227-5230.

Additional P2 building blocks, especially for compounds of formula VI are described in Schemes 11-15 below.

Synthesis and introduction of P1 building blocks.

The amino acids used in the preparation of P1 fragments are available either commercially or in the literature, see for example WO 00/09543 and WO00/59929 from Boehringer-Ingelheim.

Scheme 6 shows an example of the preparation of a sulphonamide derivative to be used as a P1 fragment, and the subsequent coupling to a Boc protected P2 building block.



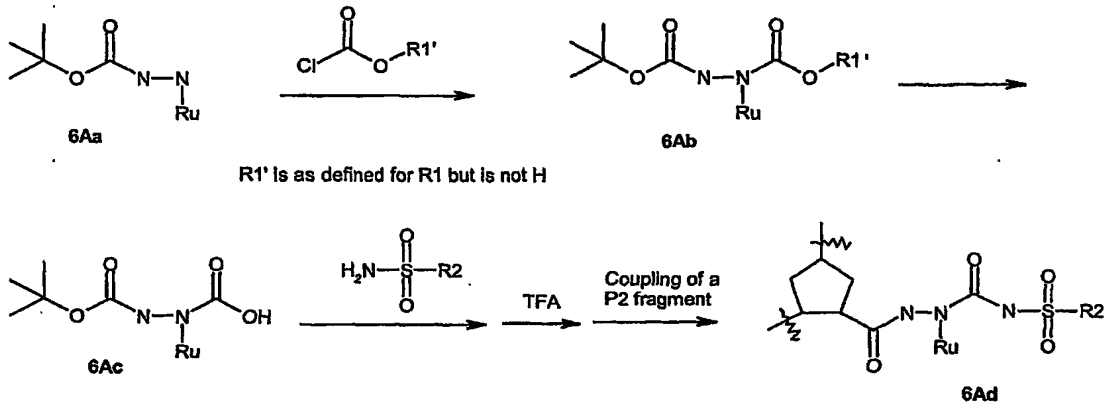

Scheme 6

The sulphonamide group can be introduced on a suitably protected amino acid (6a) by treatment of the amino acid with a coupling agent, for example N,N'-carbonyldiimidazole (CDI) or the like, in a solvent like THF followed by reaction with the desired sulphonamide (6b) in the presence of a strong base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Alternatively the amino acid can be treated with the desired sulphonamide (6b) in the presence of a base like diisopropyl

ethylamine followed by treatment with a coupling agent like PyBOP® to effect the introduction of the sulphonamide group. Removal of the amino protecting group by standard methods and subsequent coupling to a P2 building block, prepared as described above, using standard methods for amide bond formation, like with a coupling agent as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) in the presence of a base such as diisopropylamine in a solvent like dimethylformamide, gives Boc protected P2-P1 construct (6e). Alternatively, the sulphonamide group can be introduced at a later stage of the synthesis, for example as the last step. In this case the carboxylic acid is appropriately protected, for example as the methyl ester, and appropriately deprotected, for example with aqueous lithium hydroxide, prior to the coupling of the sulphonamide group.

P1 building blocks for the preparation of compounds according to general formula I and VI wherein A is an ester or an amide can be prepared by reacting amino acid (6a) with the appropriate amine or alcohol respectively under standard conditions for amide or ester formation. Compounds according to general formula I wherein A is $CR^4R^{4'}$ can be prepared by coupling of the appropriate P1 building block to the P2 building block as described in Oscarsson et al Bioorg Med Chem 2003 11(13) 2955-2963 and PCT/EP03/10595 filed 23.09.2003, the contents of which are incorporated by reference.

Compounds comprising an azapeptide P1 residue, *i.e.* Q is NRu in general formula I, VI, X and XI can be prepared by using a suitable P1 aza-amino acyl moiety in the coupling to the P2 fragment. The preparation of aza-amino acyl moieties is described by M. D. Bailey et al. in J. Med. Chem., 47, (2004), 3788-3799, and an example is shown in scheme 6A.



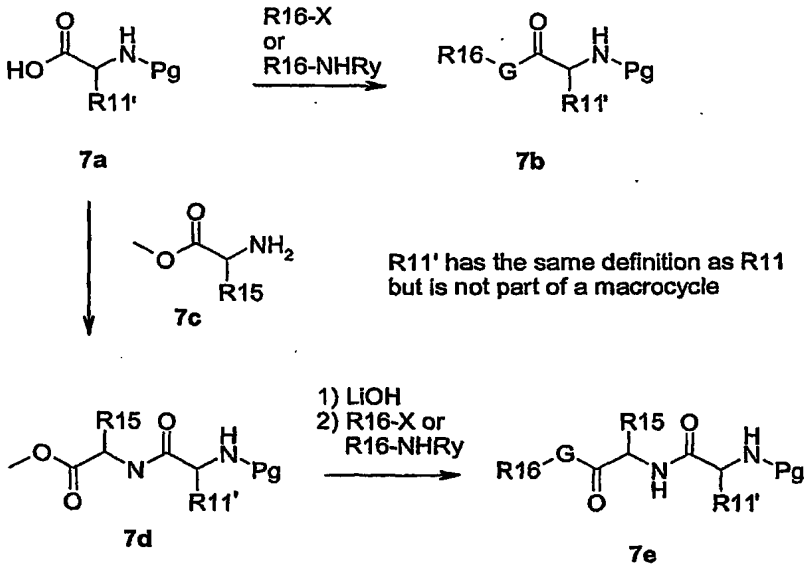

Scheme 6A

Incorporation of the appropriate N-linked side chain, Ru, on commercially available tert-butylhydrazine can be performed for example by a reductive amination reaction with the appropriate aldehyde or ketone as described in scheme 19 below which produces the N-alkylated carbazate (6Aa). Condensation of 6Aa with a desired chloroformate in the presence of a base like triethylamine or diisopropylethylamine in a solvent like THF provides 6Ab. The R1' moiety can then optionally be removed using the appropriate conditions depending on the specific R1', such as catalytic hydrogenation for R1' being benzyl, which gives the corresponding acids. Subsequent reaction of the afforded acid with a desired sulphonamide derivative as described in scheme 6 yields sulphonamide capped building blocks. Alternatively, reaction of carbazate 6Aa with an isothiocyanate, R3-N=C=O, provides building blocks for the preparation of compounds according to general formula I, VI, X or XI wherein A is CONHR3.

The P2 and P3 moieties may be linked together prior to or after the introduction of the P1 building block.

Synthesis of capped building blocks

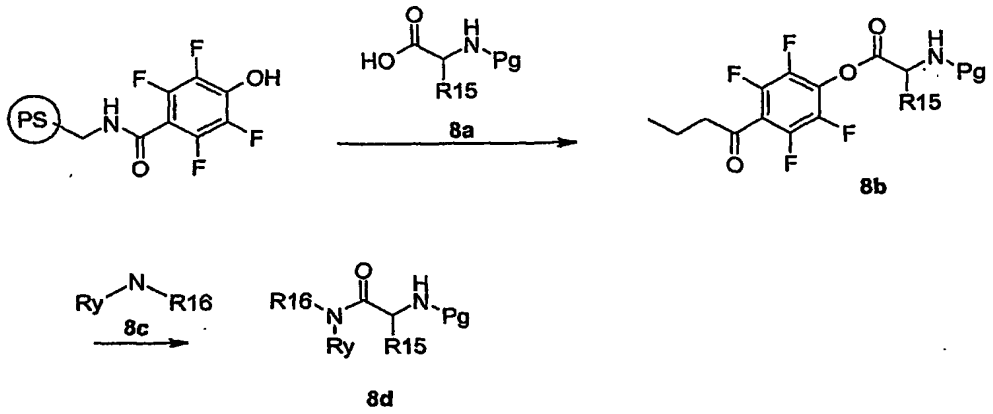
The building blocks $R^{16}$-G-P3 and $R^{16}$-G-P4-P3 can be prepared as generally depicted in scheme 7.




Scheme 7

A suitable N-protected amino acid (7a) can be coupled with an amino capping group ($R^{16}$-NHRy) using standard peptide coupling conditions like with coupling agents such as HATU, DCC, HOBt or the like in the presence of a base such as DIEA or DMAP in a solvent like dichloromethane, chloroform or dimethylformamide or a mixture thereof and ester formation conditions like providing amides i.e. G is NHRy (7b). Alternatively, reaction of amino acid (7a) with a compound of general formula $R^{16}$-X where $R^{16}$ is as defined above and X is a leaving group such as a halide, in the presence of a base like cesium carbonate or silver (I) oxide provides esters, i.e. G is O (7b). On the other hand, amino acid (7a) can be coupled to a second, suitably O-protected, amino acid (7d) using standard peptide coupling conditions as described above, providing (7e). Displacement of the ester group with a suitable capping group (7b) provides fragment (7f) useful for the preparation of compounds according to the present invention wherein m and n are 1.

When G is N-Ry, the capped P3 or P2 building block can also be prepared on solid support as exemplified in Scheme 8.

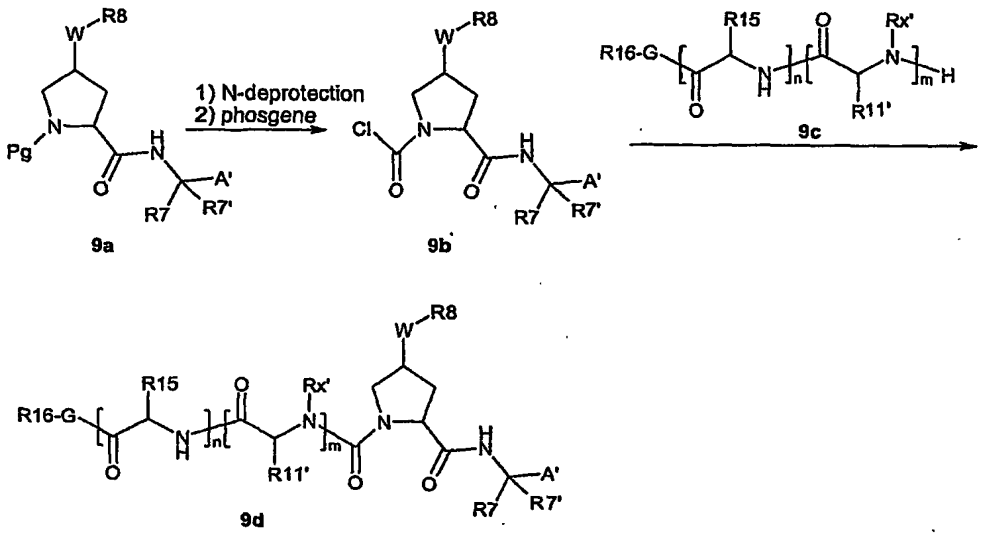



Scheme 8

An appropriate N-protected, for example Boc protected, amino acid (8a) can be immobilized on a solid support, here exemplified by Agronaut resin PS-TFP, by reacting the amino acid with the desired solid support in the presence of coupling reagent like N,N'-diisopropylcarbodiimide and a base like DMAP in a solvent like dichloromethane and dimethylformamide. The immobilized amino acid can then be cleaved from the support with a suitable capping group (8c) thus giving fragments useful for the preparation of compounds according to the present invention wherein m or n is 1. Optionally the amino protecting group can be removed followed by coupling of an appropriate amino acid using standard methods thus providing fragments useful for the preparation of compounds according to the present invention wherein m and n are 1.

Coupling of a capping group or a capped building block to the P2-P1 construct

The $R^{16}$-G, $R^{16}$-G-P3 or $R^{16}$-G-P4-P3 building block linked via a urea functionality to the P2-P1 construct, can be introduced as depicted in scheme 9, which illustrates the technique with a variant in which P2 is a heterocyclic residue.



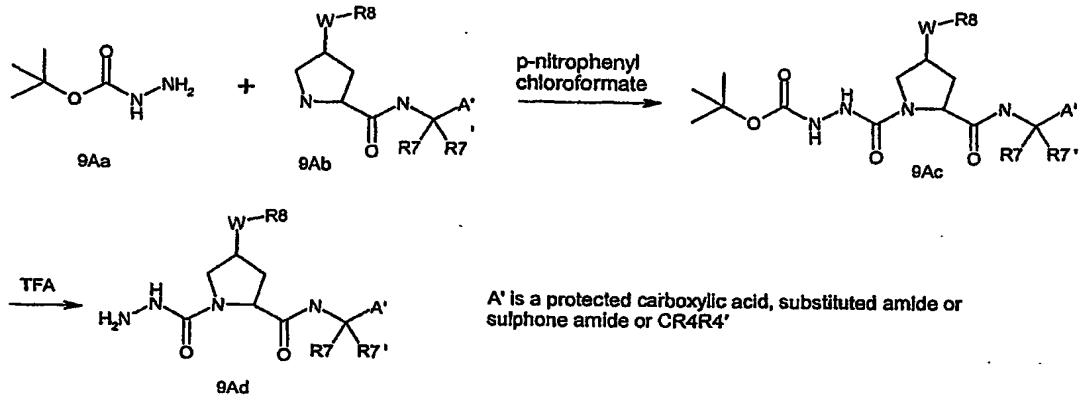

Rx' and R11' have the same definitions as Rx and R11 respectively but are not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or sulphone amide or CR4R4'.

Scheme 9

A chlorocarbamate group can be formed onto the ring amine of the P2-P1 construct (9a) by removal of the amine protection group by standard procedures, like acidic treatment with for example TFA in dichloromethane or the like when the Boc group is used, followed by reaction of the free amine with phosgene in toluene in the presence of a base such as sodium hydrogen carbonate or triethylamine in a solvent like tetrahydrofuran. Subsequent reaction of the formed electrophilic center with the amino group of a $R^{16}$-$NH_2$, $R^{16}$-NH-$NH_2$, $R^{16}$-G-P3 or $R^{16}$-G-P4-P3 building block (9c) in a solvent like dichloromethane in the presence of a base like sodium hydrogen carbonate provides (9d). Compounds of general formula (I) wherein E is C=S, S(=O) or $S(=O)_2$ can be prepared according to the above procedure but with the use of reagents like thiocarbonyl diimidazole, thionyl chloride or sulphuryl chloride respectively instead of phosgene.

Compounds containing a hydrazine moiety linked to the P2 unit, *i.e.* X is –NRjNRj- in general formula I or T is NRd in general formula VI, or when the P3 and P4 units are absent than G is NRjNRj, can be prepared as depicted below. Scheme 9A shows the

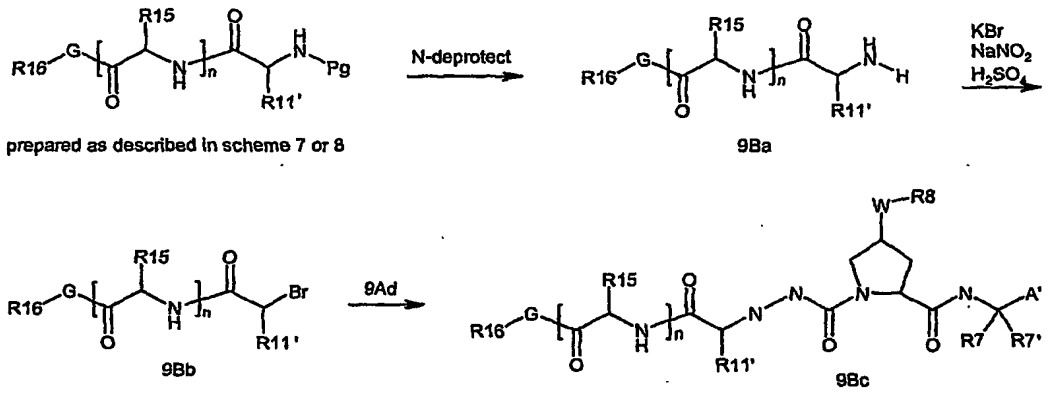
introduction of a hydrazine derivative to a 5-membered heterocyclic P2 building block.




Scheme 9A

Reaction of tert-butyl carbazate (9Aa), optionally alkyl substituted on one or both nitrgogens, with p-nitrophenyl chloroformate in the presence of a base like sodium hydrogen carbonat followed by addition of the P2 building block (9Ab) provides the 9Ac. The phosgene method described in scheme 9 can alternatively be used to effect the linkage of the fragments 9Aa and 9Ab. Optional removal of the boc group by standard procedures like acidic treatment with for example TFA in a suitable solvent such as dichloromethane, provides the hydrazine containing derivative (9Ad). Alternatively, any appropriate hydrazine derivative, such as morpholin-1-ylamine, piperidin-1-ylamine or the like can be linked to 9Ab instead of the tert-butyl carbazate derivative.

The achieved compound can then be further extended by cuopling of a P3 or P4-P3 building block to the primary amine of compound 9Ad for example as shown in scheme 9B.

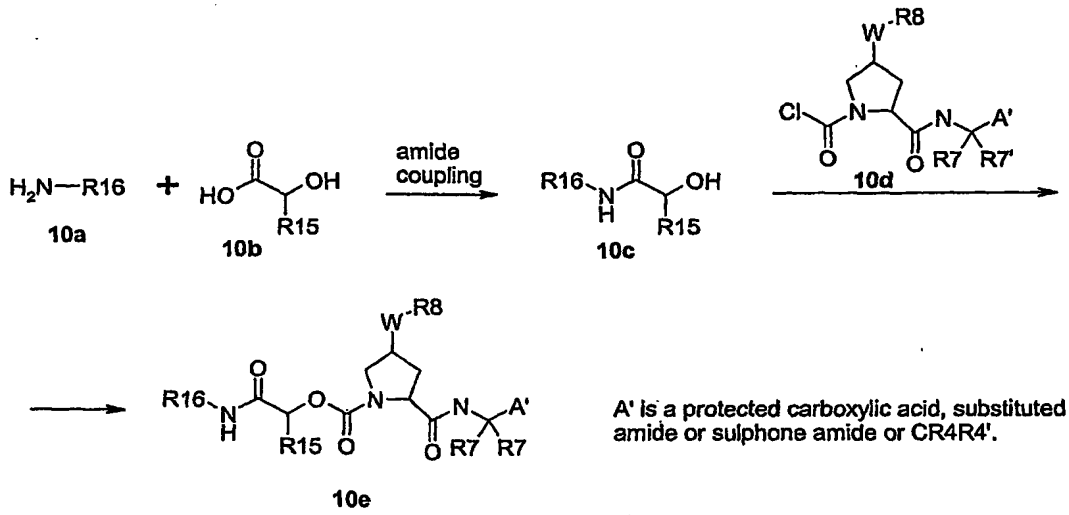



R11' has the same definition as R11 but is not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or sulphone amide or CR4R4'

Scheme 9B

Treatment of the α-amino compound (9Ba) with sodium nitrite, potassium bromide and sulphuric acid (Yang *et al.* J. Org. Chem. (2001), 66, 7303-7312) provides the corresponding α-bromo compound (9Bb) which upon reaction with the above described derivative (9Ad) provides the hydrazine containing derivative (9Bc).

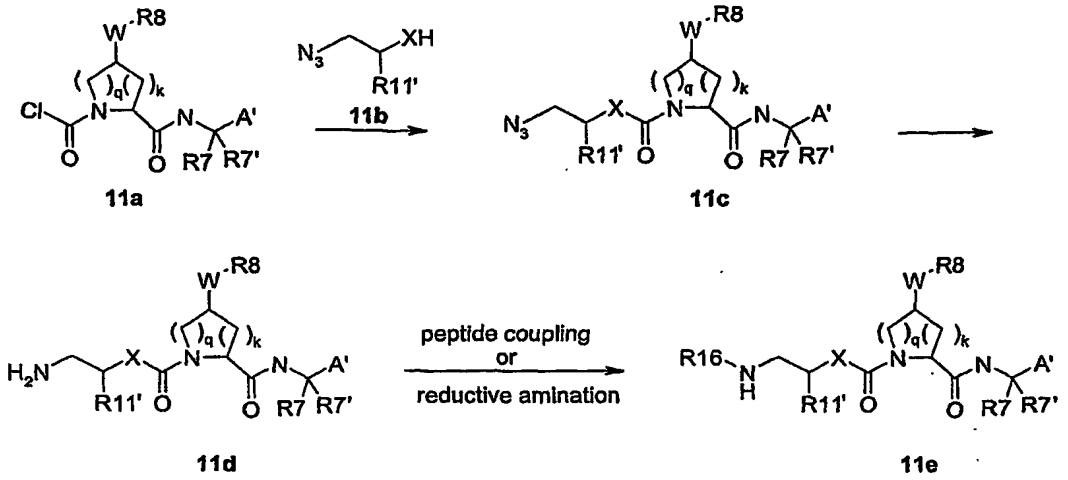
The linkage between the P2 and P3 building blocks may also be constituted of a carbamate group and a general route to such compounds is depicted in Scheme 10, which illustrates the technique with a variant in which P2 is a proline derivative.




Scheme 10

The desired, optionally protected, amino capping group (10a) is coupled to a hydroxy acid (10b) using standard peptide coupling techniques followed by reaction with the electrophilic P2 building block (10d) described above and optional deprotection provides construct (10e).

Compounds lacking a carboxy group in the P3 unit can be prepared as illustrated in Scheme 11, which illustrates the technique as applied to a compound of Formula I

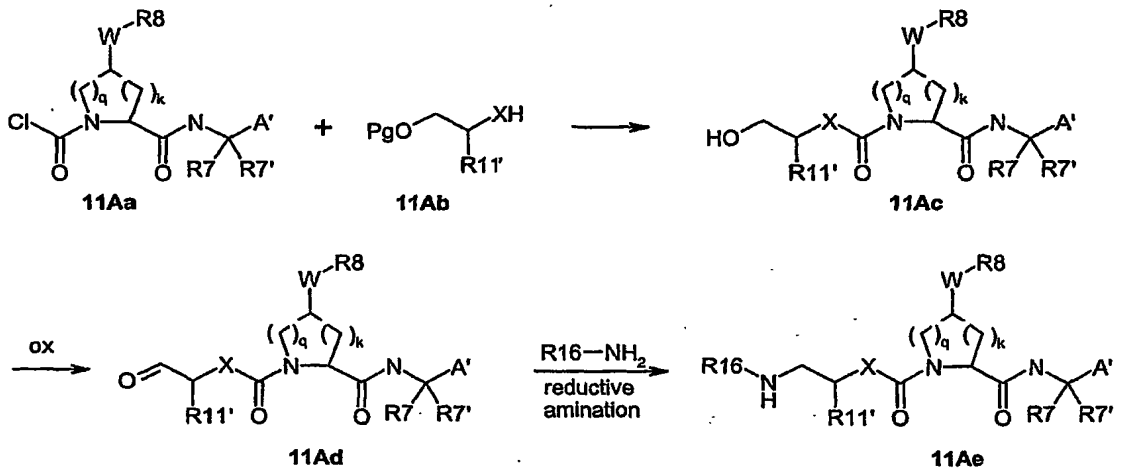



R11' has the same definition as R11but is not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or sulphone amide or CR4R4'.

Scheme 11

Chlorocarbamoyl derivative (11a) can be reacted in a displacement reaction with an azide derivative (11b), prepared by methods known from the literature, in the presence of a base like sodium hydrogen carbonate to give (11c). X is as described for general formula (I). Reduction of the azide function for example by polymer bound triphenyl phosphine in a solvent like methanol or any other suitable reduction method provides intermediate (11d) which subsequently can be reacted with an acid under peptide coupling conditions or with an amine in a reductive amination reaction providing amides and secondary amines respectively.

Scheme 11A shows an alternative route towards compounds lacking a carboxy group in the P3 unit




R11' has the same definition as R11but is not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or sulphone amide or CR4R4'.

Scheme 11A

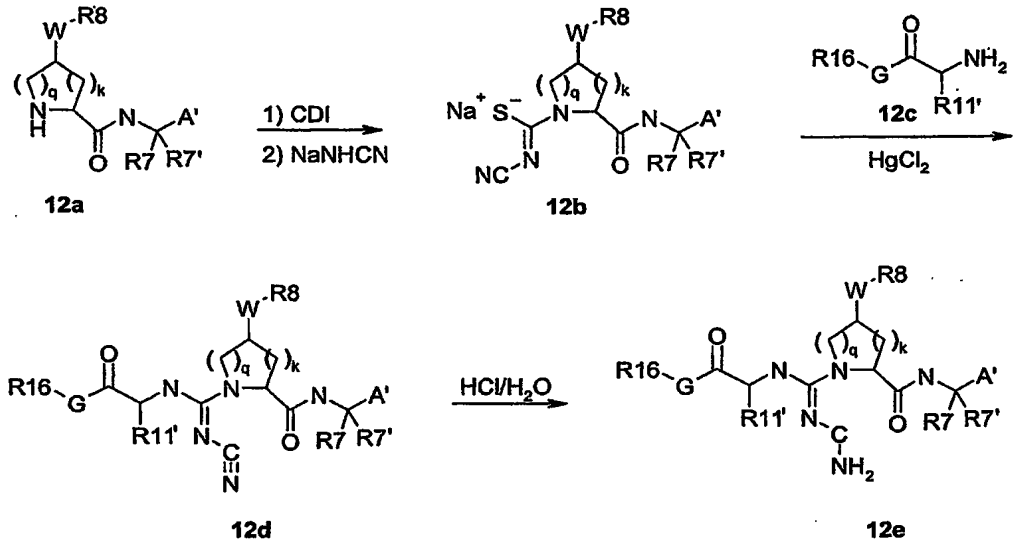
Instead of using the azide derivative (11b) in scheme 11 the corresponding, optionally protected, hydroxy derivative (11Ab) can be used in the displacement reaction with the chlorocarbamate (11Aa) and thus introducing a primary alcohol. The alcohol (11Ac) can then, after optional deprotection, be oxidized with a suitable oxidizing agent like for example Dess-Martin periodinane to form the corresponding aldehyde. Reaction of the aldehyde with a desired amine in a reductive amination reaction using a reagent like for example polystyrene bound cyanoborohydride in a solvent like THF provides amine derivatives (11Ae).

Alternatively alcohol (11Ac) can be reacted with a suitable acylating or alkylating agent under the appropriate conditions to provide ester and ether compounds respectively, i.e. G is O in general formula (I).

Subsequent reaction of the formed alcohol with a suitable acylating or alkylating agent using the appropriate conditions provides the ester and ether compounds respectively, i.e. G is O in general formula (I).

Although Figure 11 and 11 A have been described with reference to a compound of Figure I, it will be readily apparent that corresponding methodology is applicable for compounds of the Formula VI.

Alternatively the linkage between the P2 and P3 building blocks can be via a guanidine group and a general route to such compounds is depicted in Scheme 12.




R11' has the same definition as R11but is not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or sulphone amide or CR4R4'.

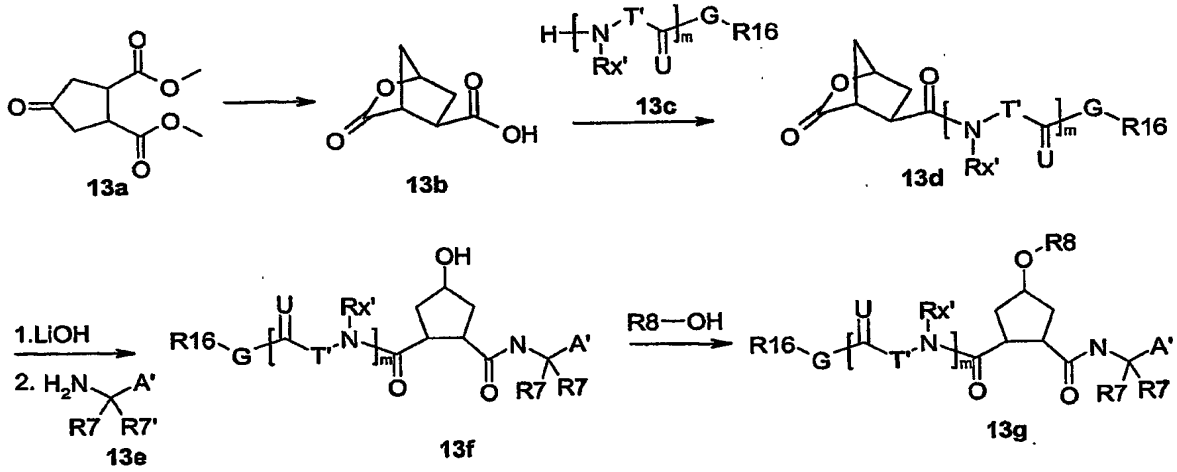
Scheme 12

Treatment of the P2-building block (12a) with thiocarbonyl diimidazole or the like in a solvent like dimethylformamide followed by condensation with sodium cyanamide in a solvent like ethanol affords the thiolate intermediate (12b). Reaction of intermediate (12b) with the desired building block, here shown as a capped P3 building block (12c) provides the cyanoguanidine derivative (12d). Other building blocks, $R^{16}$-G or $R^{16}$-G-P4-P3, can alernatively be coupled to the intermediate (12b). Hydrolysis of the cyano group by treatment of (12d) with diluted hydrochloric acid gives the guanylurea derivative (12e).

When R7, R7' and A' contains functional groups, these are suitably protected by methods recognized by persons skilled in the art, see for example Bodanzky or Greene cited above.

Carbocyclic P2 building blocks

A typical route to saturated, carbocyclic P2 bluidling blocks towards compounds of formula VI is shown in Scheme 13, which illustrates the technique with a variant wherein q' is 0 and k is 1.



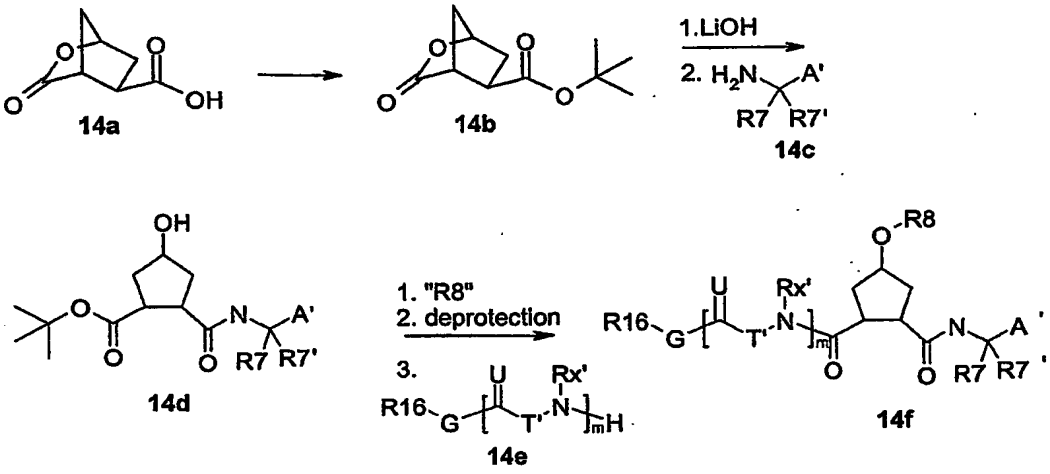

Rx' and T' have the same definitions as Rx and T respectively but are not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or sulphone amide or CR4R4'.

Scheme 13

The saturated cycloalkyl scaffold (13b) can be prepared, for example, from 3,4-bis(methoxycarbonyl)cyclopentanone (13a), described by Rosenquist et al. in Acta Chem. Scand. 46 (1992) 1127-1129 by reduction of the keto group with a reduction agent like sodium borohydride in a solvent like methanol followed by hydrolysis of the esters and finally ring closure in acetic anhydride in the presence of pyridine. The provided bicyclic acid (13b) can then be coupled to the amine function of the desired P3 fragment (13c), P3-P4 fragment or capping group $R^{16}$-NHRy, using conventional

peptide coupling conditions like with HATU and diisopropyl amine in a solvent like dimethyl formamide, giving (13d). Lactone opening of (13d) with for example lithium hydroxide provides the acid which subsequently can be coupled to the amino group of a P1 building block or a precursor of a desired P1 fragment (13e), using conventional peptide coupling conditions. The $R^8$-substituent of the carbocycle can be introduced for example by a Mitsunobu reaction with the appropriate alcohol as described above or by any other suitable method previously described. When $R^7$, $R^{7'}$ and A' contains functional groups, these are optionally suitably protected by methods recognized by persons skilled in the art, se for example Bodanzky or Greene cited above.

Scheme 14 shows an alternative route towards saturated compounds of formula VI where the building blocks are introduced in the reversed order, i.e. the P1 fragment is introduced before the capping group, P3 or P3-P4 building block.




Rx' and T' have the same definitions as Rx and T respectively but are not part of a macrocycle. A' is a protected carboxylic acid, substituted amide or sulphone amide or CR4R4'.

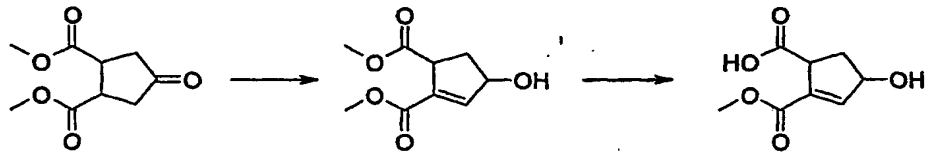
Scheme 14

Protection of the acid group of (14a) for example as the tert- butyl ester by treatment with di-tert- butyl dicarbonate in the presence of a base like dimethylaminopyridine and triethylamine in a solvent like dichloromethane provides ester (14b). Lactone

opening and coupling of a P1 building block (14c) as described in scheme 13 or directly by the amine group of the P1 fragment provides (14d). Introduction of $R^8$-substituent as described above followed by removal of the acid protection group by subjecting the ester to acidic conditions like trifluoroacetic acid and triethylsilane in a solvent like methylene chloride and finally coupling of the P3 building block (14e), P3-P4 building block or capping group $R^{16}$-NHRy, as described above provides (14f). When $R^7$, $R^{7'}$ and A' contain functional groups, these are optionally suitably protected by methods recognized by persons skilled in the art, see for example Bodanzky or Greene cited above.

An unsaturated P2 building block towards the preparation of compounds of formula VI can be prepared as illustrated with cyclopentene below.

The cyclopentene scaffold is typically prepared as described in scheme 15.

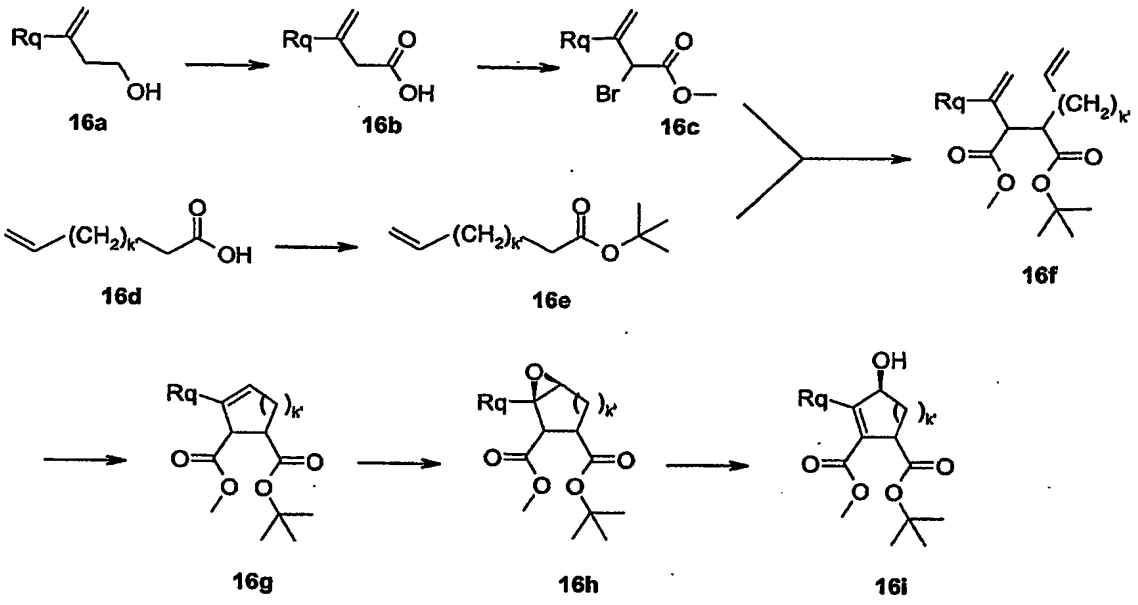



15a 15b 15c

Scheme 15

A bromination-elemination reaction of 3,4-bis(methoxycarbonyl)cyclopentanone (15a) as described by Dolby et al. in J. Org. Chem. 36 (1971) 1277-1285 followed by reduction of the keto functionality with a reduction agent like sodium borohydride provides the unsaturated hydroxy compound (15b). Selective ester hydrolysis using for example lithium hydroxide in a solvent like a mixture of dioxane and water provides hydroxy substituted monoester derivative (15c).

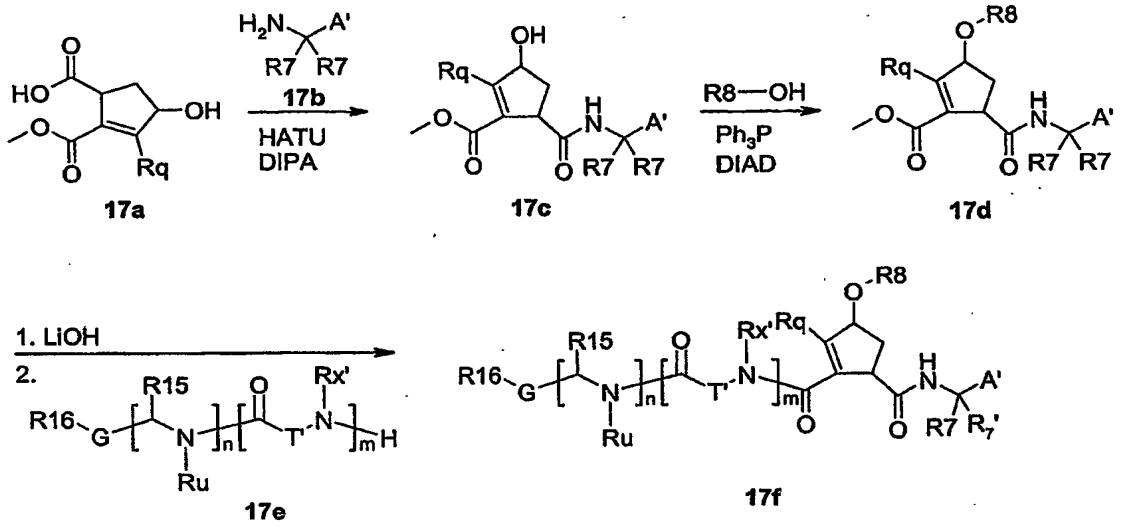
A P2 building block wherein Rq is other than hydrogen, such as a methylated cyclopentene scaffold can be prepared as shown in scheme 16.




Scheme 16

Oxidation of commercially available 3-methyl-3-buten-1-ol (16a) by the use of an oxidation agent like pyridinium chlorochromate followed by treatment with acetyl chloride, bromine and methanol provides the α-bromo ester (16c). The afforded ester (16c) can then be reacted with the enolate (16e), achieved for example by treatment of the corresponding tert-butyl ester with a base such as lithium diisopropyl amide in a solvent like tetrahydrofuran, to give the alkylated compound (16f). The tert-butyl ester (16e) can be prepared by treatment of the corresponding commercially available acid (16d) where k' is 1 to 3 with di-tert-butyl dicarbonate in the presence of a base like dimethylaminopyridine. Cyclisation of (16f) by an olefin metathesis reaction performed as described above provides cyclopentene derivative (16g). Stereoselective epoxidation of (16g) can be carried out using the Jacobsen asymmetric epoxidation method to furnish the epoxide (16h). Finally, addition of a base like DBN (1,5-diazabicyclo-[4.3.0]non-5-ene) yields the alcohol (16i). Optionally the double bond of compound (16i) can be reduced for example by catalytic hydrogenation using a catalyst like palladium on carbon which provides the corresponding saturated compound.

The afforded cyclic scaffolds can then be used, as described above, to complete the inhibitor sequence. An example is shown in scheme 17.




Rx' and T' have the same definitions as Rx and T respectively but are not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or sulphone amide or CR4R4'.

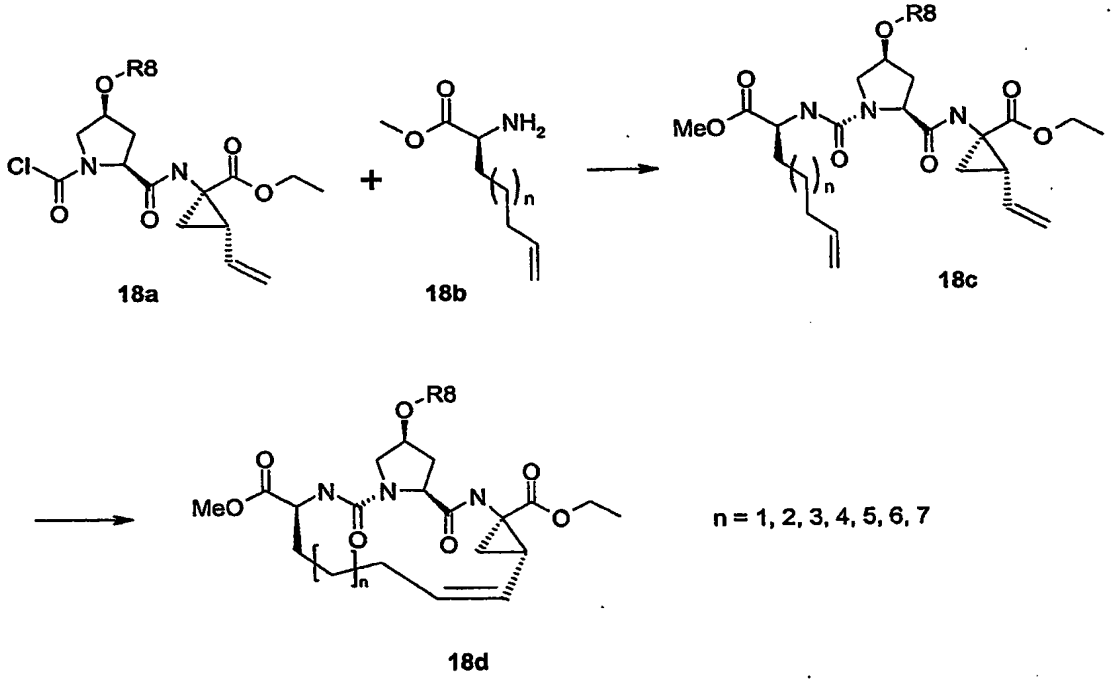
Scheme 17

The amino group of a P1-building block or a suitable precursor thereof (17b) can be coupled to the acid of the cyclopentene derivative (17a) using standard amide coupling conditions such as using HATU in the presence of a base like diisopropyl phenylamine or the like, followed by introduction of the $R^8$-substituent for example by Mitsunobu conditions as described above to provide (17d). Hydrolysis of the remaining ester and subsequent amide coupling of a desired P3 or P3-P4 building block (17e) optionally followed by manipulations of the P1 part provides cyclopentene containing compounds (17f) according to general formula VI. When $R^7$, $R^{7'}$ and A' contain functional groups, these are optionally suitably protected by methods recognized by persons skilled in the art, see for example Bodanzky or Greene cited above.

Formation of macrocyclic compounds

Compounds according to the present invention wherein an alkylene chain extending from the $R^7/R^{7'}$ cycloalkyl to Rx, Rd or $R^{11}$ thus forming a macrocycle, can be prepared as described below. Suitable P1, P2 and P3 building blocks, or precursors thereof, are coupled together using the strategies described above, followed by a ring-closing reaction (macrocyclization). The substituent W-$R^8$ of the P2 building block can be incorporated via a Mitsunobu reaction as described above, before or after formation of the macrocycle or the assembly can be done with the required substituted proline analogue or carbocycle. For macrocyclic structures extending from the $R^7/R^{7'}$ cycloalkyl to $R^{11}$, P3 amino acids containing the appropriate side chain can be prepared as described in WO00/59929.

A typical route to macrocyclic compounds is shown in Scheme 18 which illustrates the technique applied to a compound having a heterocyclic P2 and a spiro-cyclopropyl P1, where the macrocycle incorporates the P3 side chain.

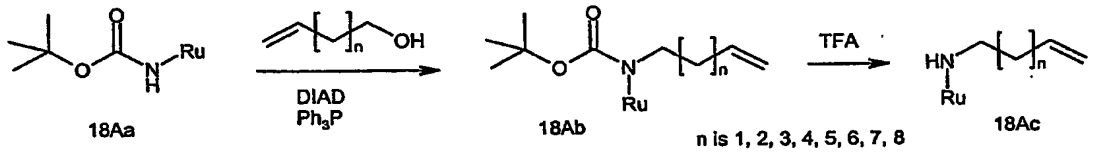



18a 18b 18c 18d

Scheme 18

Coupling of proline derivative (18a) with the appropriate, acid protected, amino acid (18b) using e.g. the phosgene conditions described above provides (18c). Formation of the macrocycle can then be carried out via an olefin metathesis reaction using a Ru-based catalyst such as the one reported by Miller, S.J., Blackwell, H.E.; Grubbs, R.H. J. Am. Chem. Soc. 118, (1996), 9606-9614, Kingsbury, J. S., Harrity, J. P. A., Bonitatebus, P. J., Hoveyda, A. H., J. Am. Chem. Soc. 121, (1999), 791-799 and Huang et al., J. Am. Chem. Soc. 121, (1999), 2674-2678. It will also be recognized that catalysts containing other transition metals such as Mo can be used for this reaction. Optionally the double bond is reduced and/or the ethyl ester is hydrolysed by standard hydrogenation and/or hydrolysation methods respectively well known in the art. Alternatively the methyl ester can be selectively hydrolysed followed by coupling of a $R^{16}$-G-P4 building block by standard peptide coupling conditions. The macrocyclisation step described in Scheme 18 can also be applied to the corresponding carbocyclic analogues described above. When the linker contains a nitrogen atom the ring closure can be carried out by reductive amination as described in WO00/59929.

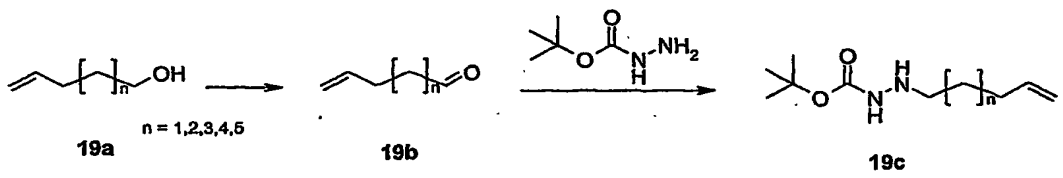
Building blocks to be used in the preparation of compounds wherein the macrocycle extends from the nitrogen in the linkage between the P2 and P3 fragments *i.e.* X is NRx in general formula I, or in the preparation of compounds wherein the P3 and P4 fragments are absent, *i.e.* m and n are 0 and G is NRj in general formula I and VI, can typically be prepared as outlined in scheme 18A.




Scheme 18A

Carbamate 18Aa, which is commercially available or is readily prepared for instance by reaction of the desired alkyl amine with di-tert-butyl dicarbonate, can be reacted with an appropriate *ω*–unsaturated alcohol under Mitsunobu conditions to provide the alkylated carbamate (18Ab). Subjection of 18Ab to acidic conditions like for example treatment with trifluoroacetic acid in a solvent like dichloromethane gives the free amine (18Ac) which can be linked to a P2 fragment using any of the previously described strategies.

Macrocyclic structures containing a hydrazine group *i.e.* X is NRjNRj or T is NRd in general formula I and VI respectinely, or m and n are 0 and G is NRjNRj, in general formula I and VI, can be prepared by linking a suitably N-alkylated carbazate derivative to the P2 fragment. Alkylated carbazate derivatives can be prepared, for example, as described in Scheme 19.

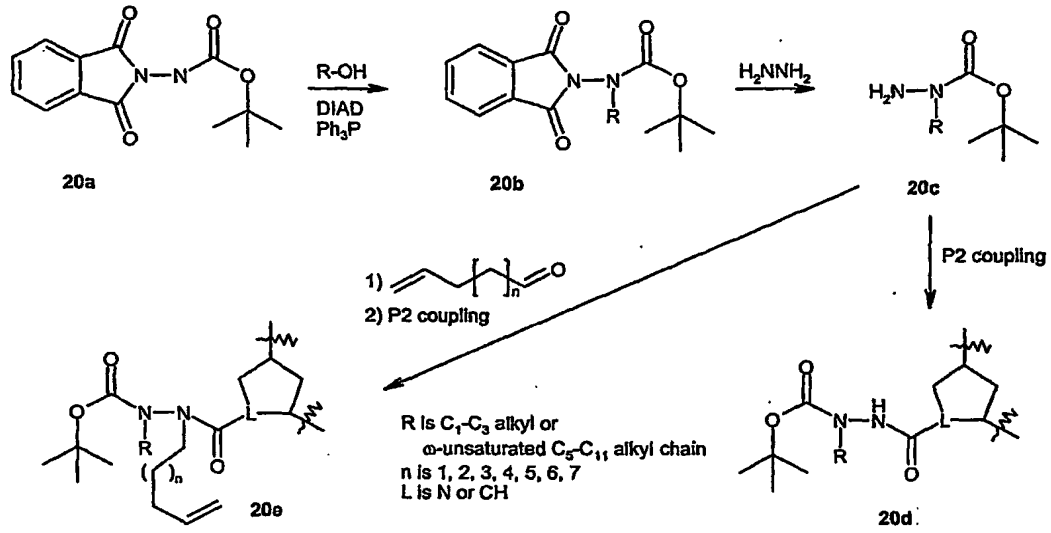



Scheme 19

Oxidation of the appropriate alcohol (19a) effected by a suitable oxidation method like for example with N-methyl morpholine oxide and tetrapropylammonium perruthenate in a solvent like dichloromethane provides aldehyde (19b). Reductive alkylation of tert-butyl carbazate with the afforded aldehyde gives the desired N-alkylated building block (19c). Alternatively, any desired hydrazine derivative such as morpholin-1-ylamine, piperidin-1-ylamine or the like can be used instead of tert-butyl carbazate in the reaction with aldehyde 19b.

Scheme 20 illustrates synthetic sequences to building blocks suitable for the preparation of compounds wherein the "outer" nitrogen of the hydrazine group is

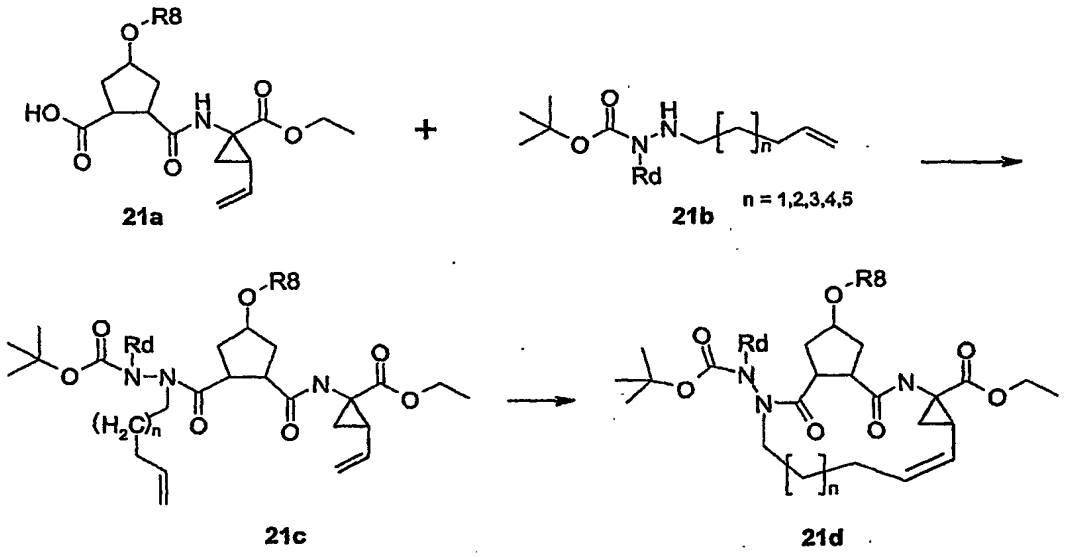
alkylated, either with an $\omega$-unsaturated alkyl chain appropriate for subsequent macrocycle formation or with any other suitable alkyl group.




Scheme 20

Reaction of a suitably protected hydrazine derivative, for example (1,3-dioxo-1,3-dihydro-isonidol-2-yl)-carbamic acid tert-butyl ester (20a), which can easily be prepared by a person skilled in the art, with a desired alcohol, R-OH, under Mitsunobu conditions provides N-alkylated hydrazine compound (20b). Removal of the phtalimido group effected by treatment with hydrazine or a derivative thereof like hydrazine hydrate or hydrazine acetate provides the carbazate (20c). The afforded primary amine can then either be be coupled to any desired P2 fragment using any of the methods previously described to give 20d or alternatively it can be further alkylated using for example the reductive amination method described in scheme 19 followed by coupling to a P2 fragment as previously described to give 20e .

Scheme 21 exemplifies the coupling of a hydrazine containing P3 building block to a cyclopentane scaffold followed by macrocyclisation.




Scheme 21

Coupling of the carbazate derivative (21b) to the P2-P1 building block (21a) using standard peptide coupling conditions provides intermediate (21c). Ring closure of (21c) by an olefin metathesis reaction as described in scheme 18 gives the macrocyclic compound (21d).

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York, 1981), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoracetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl, and the like, carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl,

3,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butoxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like; alkyl gropus such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Favoured N-protecting groups include formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butoxycarbonyl (BOC) and benzyloxycarbonyl (Cbz).

Hydroxy protecting group as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)). Hydroxy protecting groups comprise substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl and other lower alkyl ethers, such as isopropyl, ethyl and especially methyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; and esters prepared by reacting the hydroxyl group with a carboxylic acid, for example, acetate, propionate, benzoate and the like.

In treating conditions caused by flavivirus such as HCV, the compounds of formula I or VI are typically administered in an amount to achieve a plasma level of around 100 to 5000 nM, such as 300 to 2000 nM. This corresponds to a dosage rate, depending on the bioavailability of the formulation, of the order 0.01 to 10 mg/kg/day, preferably 0.1 to 2 mg/kg/day. A typical dosage rate for a normal adult will be around 0.05 to 5 g per day, preferably 0.1 to 2 g such as 500-750 mg, in one to four dosage

units per day. As with all pharmaceuticals, dosage rates will vary with the size and metabolic condition of the patient as well as the severity of the infection and may need to be adjusted for concomitant medications.

As is good prescribing practice with antiviral therapy, the compounds of formula I are typically coadministered with other HCV therapies to avoid the generation of drug escape mutants. Examples of such additional HCV antiviral therapies include ribavirin, interferons, including pegylated interferons. Additionally a number of nucleoside analogues and protease inhibitors are in the development and will be amenable to co-administration with the compounds of the invention.

While it is possible for the active agent to be administered alone, it is preferable to present it as part of a pharmaceutical formulation. Such a formulation will comprise the above defined active agent together with one or more acceptable carriers or excipients and optionally other therapeutic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

The formulations include those suitable for rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration, but preferably the formulation is an orally administered formulation. The formulations may conveniently be presented in unit dosage form, e.g. tablets and sustained release capsules, and may be prepared by any methods well known in the art of pharmacy.

Such methods include the step of bringing into association the above defined active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a compound of Formula I or VI or its pharmaceutically acceptable salt in

conjunction or association with a pharmaceutically acceptable carrier or vehicle. If the manufacture of pharmaceutical formulations involves intimate mixing of pharmaceutical excipients and the active ingredient in salt form, then it is often preferred to use excipients which are non-basic in nature, i.e. either acidic or neutral. Formulations for oral administration in the present invention may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion and as a bolus etc.

With regard to compositions for oral administration (e.g. tablets and capsules), the term suitable carrier includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, stearic acid, glycerol stearate, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring or the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

The compounds of formula I or VI can form salts which form an additional aspect of the invention. Appropriate pharmaceutically acceptable salts of the compounds of formula I include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, isethionate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanate, glucoheptanate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, proprionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-napthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, phosphoric and sulphonic acids.

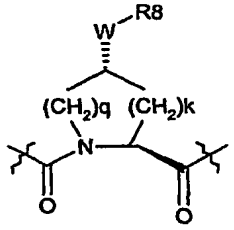
Prodrugs of the compounds of formula I are those compounds which following administration to a patient release a compound of the formula I in vivo generally following hydrolysis in the gut, liver or plasma. Typical prodrugs are pharmaceutically acceptable ethers and especially esters (including phosphate esters) of hydroxy functions, pharmaceutically acceptable amides or carbamates of amine functions or pharmaceutically acceptable esters of carboxy functions. PreferredPharmaceutically acceptable esters include alkyl esters, including acetyl, ethanoyl, butyryl, t-butyryl, stearyl and pivaloyl, phosphate esters and sulphonic esters (ie those derived from $RSO_2OH$, where R is lower alkyl or aryl). Pharmaceutically acceptable esters include

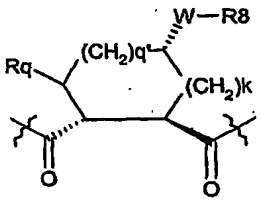
lower alkyl ethers and the ethers disclosed in WO00/47561, especially methoxyaminoacyl and ethoxyaminoacyl.

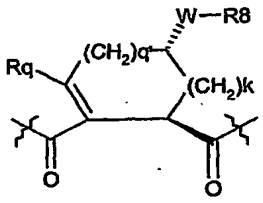
The compounds of the invention have various steric centres and the invention extends to racemates and enantiomers at each of these steric centres.

Typically, the stereochemistry of the groups corresponding to the P3 and P4 side chains (ie $R^{15}$ and/or $R^{11}$) will correspond to an L-amino acid configuration, although the invention also extends to D-isomers at one or both of these centres. It is noteworthy that the L configuration is active nothwithstanding that the P3 and P4 are typically translated one atom relative to a conventional polypeptide.

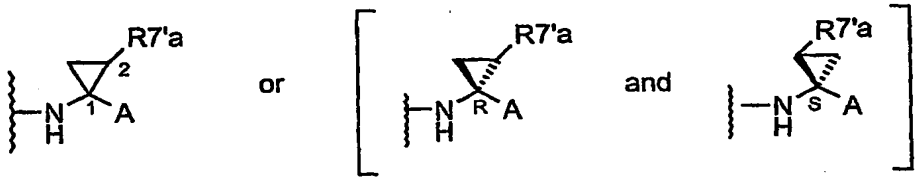
The stereochemistry of the backbone component of the cyclic P2 group (i.e. spanning the carbonyl of the P1 amide bond and the carbonyl or E extending of P3 will typically correspond to L-proline. The stereochemistry of the P2 ring atom to which W is bonded is typically as shown:



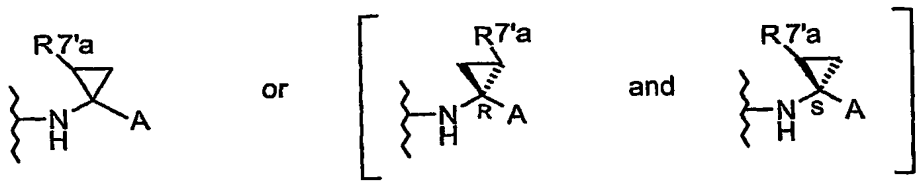



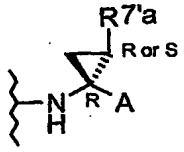

In compounds of the invention wherein $R^7$ and $R^{7'}$ together define a spiroalkyl group, such a spiro-cycloalkyl will typically comprise an $R^{7'a}$ substituent on the spiro-cyclopropyl ring which is is orientated syn to A:



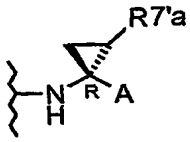
or anti to A:




Conveniently, the spiro carbon of such a spiro-cyclopropyl ring has the R configuration:



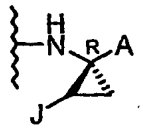

Conveniently an $R^{7'a}$ substituent on a spiro-cyclopropyl ring adjacent to A is in a syn orientation in the following absolute configuration:



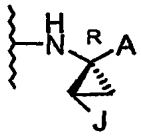

Particularly preferred variants have $R^{7'a}$ include ethyl, hence the asymmetric carbon atoms at position 1 and 2 have the R, R configuration.

Alternative preferred $R^{7'a}$ include vinyl, hence the asymmetric carbon atoms at position 1 and 2 have the R, S configuration.

Where the compound of the invention is a macrocycle comprising a J group, J is preferably a diastereomer represented by partial structures (i) or (ii):




or




J syn to the amide (i) J syn to A (ii)

especially where J is syn to A.

Detailed description of the embodiments

Various embodiments of the invention will now be described by way of illustration only with reference to the following non-limiting examples.

Example 1

7-Methoxy-2-phenyl-quinolin-4-ol (1)

To a stirred round bottled flask with toluene (100 mL) ethyl benzoyl acetate (18.7 g, 97 mmol) and *m*-anisidine (12 g, 97 mmol) was added. 4 M HCl in dioxane (0.5 mL) was added and the reaction mixture was refluxed for 6 h (140 °C). The mixture was co-evaporated with toluene. To the crude mixture diphenyl ether (50 mL) was added and the mixture was heated to 280 °C for 2 h. When the theoretical amount ethanol (6 mL) was collected in a Dean Stark trap the heating was stopped and the mixture was cooled to rt. The crude mixture was dissolved in $CH_2Cl_2$ (100 mL) and stirred for 30 min. The formed precipitate was filtered off and dried which gave 1 (4.12 g, 16.4 mmol, 17 %): pale yellow powder.

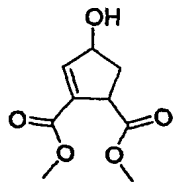
$^1$H (300 MHz, DMSO-$D_6$): δ 3.8 (s, 3H), 6.24 (s, 1H), 6.88-6.96 (dd, 1H, *J* = 9.07 Hz, *J* = 2.47 Hz), 7.19 (d, 1H, *J*=2.19 Hz), 7.56 (t, 3H, *J* = 2.19 Hz), 7.8 (dd, 2H, *J* = 7.14 Hz, *J* = 2.19 Hz), 8.0 (d, 1H, *J* = 9.06 Hz); $^{13}$C (75.5 MHz, DMSO-$D_6$): δ 55.3, 99.6, 106.9, 113.1, 119.1, 126.4, 127.5, 128.8, 130.2, 134.1, 142.2, 149.4, 161.8, 176.4.

Example 2

(Rac)-4-oxocyclopent-2-ene-1, 2-dicarboxylic acid dimethyl ester (2)

(1*R*, 2*S*)-4-oxo-cyclopentane-1, 2-dicarboxylic acid dimethyl ester (4.8 g, 23.8 mmol) and $CuBr_2$ (11.9 g, 53.2 mmol) were dissolved in dry THF (70 mL) and the mixture was refluxed for two hours at 90 °C. The formed CuBr was filtrated off and the organic phase was concentrated. $CaCO_3$ (2.7 g, 27.2 mmol) and DMF (70 mL) were added and the mixture was held at 100 °C for one hour. The dark brown mixture was poured over ice (35 g) and the formed precipitate was filtrated off. The aqueous layer was extracted with ethyl acetate (1 x 300mL + 3 x 150 mL). The organic phases were dried, filtrated and concentrated. Purification by flash chromatography (toluene/EtOAc 9:1) gave 2 (2.1 g, 45 %) as yellow crystals

Example 3




((1*S*,4*R*) & (1*R*,4*S*))-4-hydroxy-cyclopent-2-ene-1,2-dicarboxylic acid dimethyl ester (3)

To a cold solution (-30 °C) of 2 (3.18 g, 16.1 mmol) dissolved in MeOH (23 mL), $NaBH_4$ (0.66 g, 17.5 mmol) was added. After nine minutes the excess of $NaBH_4$ was destroyed by adding brine (80 mL). The mixture was concentrated and extracted with ethyl acetate (4 x 80 mL). The organic phases were dried, filtrated and concentrated and gave 3 (3.0 g, 92 %) as a yellow oil.

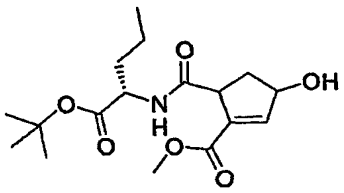
Example 4

(1*S*,4*R*) & (1*R*,4*S*)-4-hydroxy-cyclopent-2-ene-1,2-dicarboxylic acid 2-methyl ester (4)

To an ice-cold solution of 3 (3.4 g, 22 mmol) dissolved in dioxane and water (1:1, 110mL), LiOH (0.52 g, 22 mmol) was added. After two and a half hours the mixture was co-evaporated with toluene and methanol. Purification by flash chromatography (toluene/Ethyl acetate 3:1 + 1 % HOAc) gave the title compound (1.0 g, 27 %) as yellow-white crystals.

$^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 1.78-1.89 (m, 1H), 2.70-2.84 (m, 1H), 3.56-3.71 (m, 1H), 3.76 (s, 3H), 4.81-4.90 (m, 1H), 6.76-6.81 (m, 1H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta$ 38.0, 48.0, 52.4, 75.7, 137.0, 146.2, 165.0 178.4.

Example 5

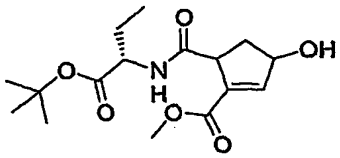



((3*S*,5*R*) & (3*R*,5*S*))-5-((*S*)-1-tert-Butoxycarbonyl-butylcarbamoyl)-3-hydroxy-cyclopent-1-enecarboxylic acid methyl (5)

To an ice cooled solution of 4 (0.20 g, 1.1 mmol) and 2-amino-pentanoic acid tert.butyl ester (0.24 g, 1.4 mmol) in DMF (7 mL), DIPEA (0.18 g, 1.4 mmol) and HATU (0.53 g, 1.4 mmol) were added. After two hours the solution was concentrated and purified using column chromatography (toluene/ethyl acetate 3:1). This gave the title compound as a yellow oil (0.22 g, 63 %).

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.84-0.96 (m, 3H), 1.14-1.39 (m, 2H), [(1.44 & 1.49) s, 9H], 1.50-1.60 (m, 1H), 1.61-1.85 (m, 1H), 1.97-2.10 (m, 1H), 2.11-2.28 (m, 1H), 3.57-3.68 (m, 1H), [(3.73 & 3.76) s, 3H], 4.30-4.50 (m, 1H), 4.63-4.73 (m, 1H), 6.80-6.95 (m, 1H), 6.95-7.00 (m, 1H).

Example 6

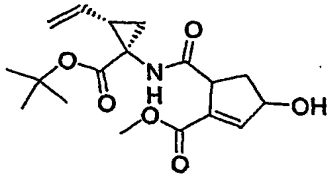


((3*S*,5*R*) & (3*R*,5*S*))-5-((*S*)-1-*tert*-Butoxycarbonyl-propylcarbamoyl)-3-hydroxy-cyclopent-1-enecarboxylic acid methyl ester (6)

Reaction of 4 (141 mg, 76 mmol) according to the method described for the preparation of 5 using L-2-amino-N-butyric acid tert.butyl ester instead of 2-amino-pentanoic acid tert.butyl ester gave the title compound as a slightly yellow oil (171 mg, 69 %).

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.89-0.98 (m, 3H), [(1.42 & 1.44) s, 9H], 1.60-1.78 (m, 1H), 1.79-1.95 (m, 1H), 1.99-2.11 (m, 1H), 2.18-2.30 (m, 1H), 3.58-3.65 (m, 1H), [3.75 & 3.78 ) s, 3 H], 4.22-4.39 (m, 1H), 4.61-4.66 (m, 1H), 6.77-6.90 (m, 1H), 6.91-6.92 (m, 1H).

Example 7

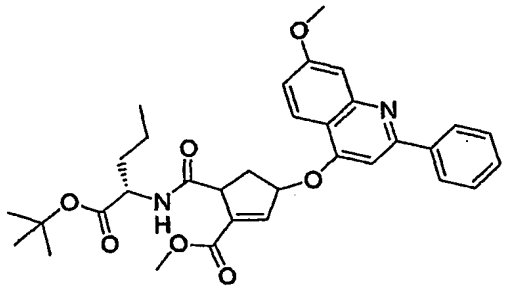


((3*S*,5*R*) & (3*R*,5*S*))-5-((1*R*,2*S*)-1-*tert*-Butoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-3-hydroxy-cyclopent-1-enecarboxylic acid methyl ester (7)

Reaction of 4 (50 mg, 37 mmol) according to the method described for the preparation of 5 using (1R, 2S)-1-amino-2-vinyl-cyclopropane carboxylic acid *tert*.butyl ester instead of 2-amino-pentanoic acid *tert*.butyl ester provided the title compound as a slightly yellow oil (50 mg, 38 %).

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ [(1.38 & 1.42) s, 9H], 1.75-1.83 (m, 1H), 2.00-2.21 (m, 3H), 3.55-3.63 (m, 1H), [(3.77 & 3.82) s, 3H], 4.20-4.38 (m, 1H), 4.65-4.80 (m, 1H), 5.13-5.20 (m, 1H), 5.22-5.38 (m, 1H), 5.60-5.82 (m, 1H), 6.95-6.96 (m, 2H).

Example 8

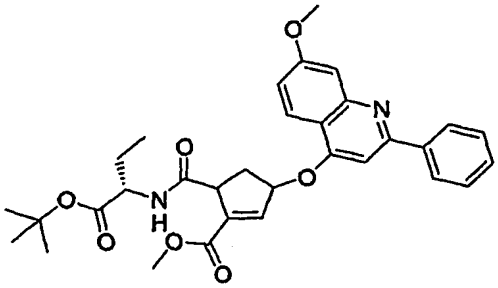


((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-tert-Butoxycarbonyl-butylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid methyl ester (8)

To an ice cooled solution of 5 (0.23 g, 0.67 mmol) in dry THF, 7-methoxy-2-phenyl-quinolin-4-ol (0.22 g, 0.88 mmol) and triphenylphosphine (0.23 g, 0.88 mmol) were added. Then DIAD (0.19 g, 0.92 mmol) was dissolved in THF (2 mL) and added dropwise to the solution. After one hour the mixture was concentrated and purified using flash chromatography (toluene/ethyl acetate 3:1). This gave the title compound as a white powder (0.30 g, 77 %).

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0,88-1.00 (m, 3H), 1.18-1.43 (m, 2H), [(1.45 & 1.50) s, 9H], 1.53-1.65 (m, 1H), 1.66-1.85 (m, 1H), 2.29-2.43 (m, 1H), 3.10-3.25 (m, 1H), [(3.79 & 3.83) s, 3H], 3.97 (s, 3H), 4.05-4.20 (m, 1H), 4.38-4.50 (m, 1H), 6.03-6.13 (m, 1H), 6.65-6.90 (m, 1H), 7.04-7.18 (m, 3H), 7.40-7.56 (m, 4H), 8.00-8.12 (m, 3H).

Example 9

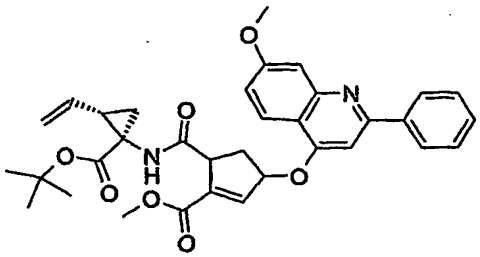


((3*R*,5*R*) & (3*S*,5*S*))--5-((*S*)-1-*tert*-Butoxycarbonyl-propylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid methyl ester (9)

Reaction of 6 (132 mg, 40 mmol) according to the method described for the preparation of 8 gave the title compound as a yellow oil (137 mg, 61 %).

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.83-0.98 (m, 3H), [(1.42 & 1.44) s, 9H], 1.65-1.78 (m, 1H), 1.80-1.97 (m, 1H), 2.30-2.40 (m, 1H), 3.05-3.20 (m, 1H), [(3.78 & 3.80) s, 3H], 3.94 (s, 3H), 3.95-4.01 (m, 1H), 4.38-4.44 (s, 1H), 6.05-6.15 (m, 1H), 6.80-6.94 (m, 1H), 7.02-7.15 (m, 3H), 7.38-7.55 (m, 4H), 7.97-8.18 (m, 3H).

Example 10

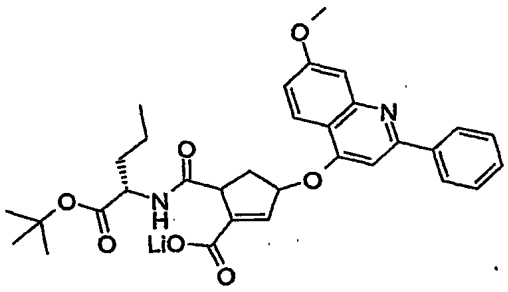


((3*R*,5*R*) & (3*S*,5*S*))-5-((1*R*,2*S*)-1-*tert*-Butoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid methyl ester (10)

Reaction of 7 (41 mg, 116 mmol) according to the method described for the preparation of 8 provided the title compound as a yellow oil.

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 1.52-1.57 (m, 1H), 1.58 (m, 9H), 1.80-1.83 (m, 1H), 2.00-2.17 (m, 1H), 2.20-2.38 (m, 1H), 3.20-3.37 (m, 1H), 3.80 (s, 3H), 3.81-3-3.98 (m, 1H), 3.99 (s, 3H), 5.12-5.20 (m, 1H), 5.22-5.40 (m, 1H), 5.63-5.80 (m, 1H), 6.05-6-20 (m, 1H), 7.00-7.21 (m, 4H), 7.40-7.58 (m, 4H), 8.02-8.18 (m, 3H).

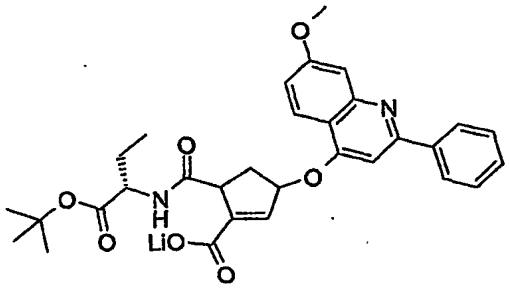
Example 11



((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-tert-Butoxycarbonyl-butylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid (11)

The methyl ester 8 (0.35 g, 0.61 mmol) was dissolved in dioxane/water (1:1, 7mL) and LiOH (0.031 g, 1.3 mmol) was added. The reaction was stirred over night and then co-concentrated. This gave the lithium salt of 11 (0.32 g, 90 %) as a brown powder.

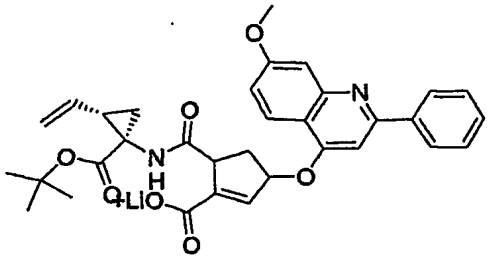
Example 12



((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-*tert*-Butoxycarbonyl-propylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid (12)

Reaction of 9 (225 mg, 40 mmol) according to the method described for the preparation of 11 provided the title compound as a yellow salt (157 mg, 72 %).

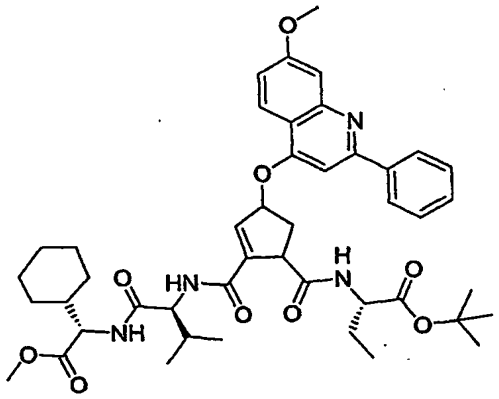
Example 13



((3*R*,5*R*) & (3*S*,5*S*))-5-((1*R*,2*S*)-1-*tert*-Butoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid (13)

Reaction of 10 (35 mg, 59 mmol) according to the method described for the preparation of 11 (33 mg, 97 %) provided the title compound as a yellow salt.

Example 14



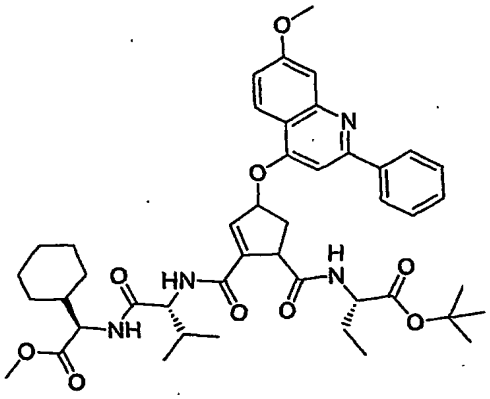
(*S*)-2-{[((1*S*,4*S*) & (1*R*,4*R*))-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid *tert*-butyl ester (14)

The acid 12 (38.4 mg, 0.070 mmol) and (2-amino-3-methyl-butyrylamino)-cyclohexyl acetic acid methyl ester (26.6 mg, 0.098 mmol) were dissolved in DMF (1.5 mL) and

cooled in an ice-bath. DIPEA (17.1 µL, 0.098 mmol) and HATU (37.4 mg, 0.098 mmol) were added. After ninety minutes the mixture was co-concentrated with toluene and methanol and then purified by flash column chromatography (toluene/ethyl acetate 6:1). Further purification was performed on HPLC (90 % MeOH + 0.2 % TEA). The diastereomeric mixture 14 was concentrated and gave a slightly yellow oil (20.6 mg, 37 %). After lyophilisation 14 was collected as a white powder.

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.93-1.02 (m, 9H), 1.03-1.25 (m, 4H), 1.44 (s, 9H), 1.65-1.86 (m, 9H), 2.05-2.10 (m, 1H), 2.22-2.40 (m, 1H), 3.05-3.20 (m, 1H), 3.77 (s, 3H), 3.98 (s, 3H), 4.18-4.22 (m, 1H), 4.38-4.60 (m, 3H), 6.01-6.10 (m, 1H), 6.61-6.70 (m, 2H), 6.80-6.85 (m, 1H), 7.05-7.18 (m, 2H), 7.40-7.58 (m, 5H), 8.00-8.13 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta$ 9.7, 18.4, 19.2, [25.9 & 26.1], [28.2 & 28.5], 29.6, 32.0, 37.3, 41.0, 46.2, 50.7, 52.4, 54.4, 55.8, 57.2, 58.5, 82.0, 82.8, 98.4, 110.2, 118.4, 120.1, 123.2, 127.9, 128.2, 128.9, 129.5, 131.2, 135.1, 135.2, 142.7, 144.2, 161.6, 164.3, 164.7, 170.9, 171.4, 172.4. MALDI-TOF *m/z* 821.56 [(M +Na)$^+$ calcd for $C_{45}H_{58}N_4NaO_9^+$ 821.41].

Example 15

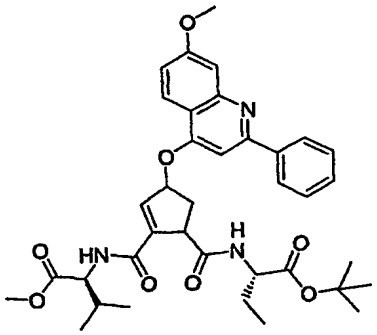


(*S*)-2-{[((1*R*,4*R* ) & (1*S*,4*S*))-2-{(*R*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid *tert*-butyl ester (15)

Reaction of 12 (20 mg, 37 mmol) according to the method described for the preparation of 14 using (2-amino-3-methyl-butyrylamino)-(R)-cyclohexyl acetic acid methyl ester instead of (2-amino-3-methyl-butyrylamino)-(S)-cyclohexyl acetic acid methyl ester, gave the title compound (19 mg, 66 %) as a white powder.

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.91-0.98 (m, 3H), 0.99-1.10 (m, 6H), 1.11-1.38 (m, 4H), [(1.43 & 1.45) s, 9H], 1-45-1.94 (m, 9H), 2.05-2.18 (m, 1H), 2.22-2.40 (m, 1H), 3.16-3.24 (m, 1H), 3.77 (s, 3H), 3.98 (s, 3H), 4.04-4.18 (m, 1H), 4.36-4.57 (m, 3H), 6.00-6.08 (m, 1H), 6.13-6.21 (m, 1H), 6.62-6.70 (m, 1H), 6.81-6.85 (m, 1H), 7.05-7.18 (m, 3H), 7.41-7.57 (m, 4H), 8.02-8.13 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta$ 9.3, 18.2, 19.0, [25.5 & 25.9], [28.0 & 28.3], 29.4, 31.4, 32.1, 35.7, 40.7, 50.4, 52.2, 54.2, 55.5, 57.0, 58.2, 81.8, 82.4, 98.2, 107.5, 115.0, 118.1, 122.9, 127.6, 128.7, 128.8, 128.9, 129.2, 135.1, 140.4, 142.2, 151.4, 161.3, 163.9, 170.4, 170.9, 171.2, 172.0. MALDI-TOF *m/z* 821.60 [(M +Na)$^+$ calcd for $C_{45}H_{58}N_4NaO_9^+$ 821.41].

Example 16



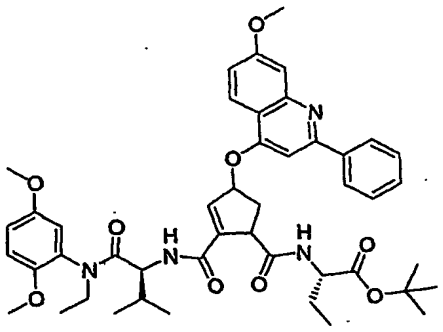
(*S*)-2-{[((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-*tert*-Butoxycarbonyl-propylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarbonyl]-amino}-3-methyl-butyric acid methyl ester (16)

Reaction of 12 (24 mg, 44 mmol) according to the method described for the preparation of 14 using D-valine methyl ester instead of (2-amino-3-methyl-

butyrylamino)cyclohexyl acetic acid methyl ester, gave the title compound (27 mg, 97 %) as a white powder.

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.82-0.99 (m, 9H), [(1.42 & 1.44) s, 9H] 1.65-1.95 (m, 2H), 2.18-2.25 (m, 1H), 2.26-2.40 (m, 1H), 3.20-3.25 (m, 1H), 3.75 (s, 3H), 3.97 (s, 3H), 4.15-4.19 (m, 1H), 4.36-4.43 (m, 1H), 4.64-4.75 (m, 1H), 6.03-6.15 (m, 1H), 6.80-6.85 (m, 2H), 7.10-7.20 (m, 3H), 7.42-7.58 (m, 4H), 8.0-8.10 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta$ 9.7, [18.2 & 19.1], 25.7, [28.1 & 28.2], 32.0, 35.6, 50.4, 52.4, 54.5, 55.7, 57.6, 81.7, 82.7, 98.4, 107.7, 115.2, 118.4, 123.2, 127.8, 129.0, 129.2, 129.5, 134.8, 135.0, 140.4, 142.5, 151.6, 159.6, [161.1 & 161.5], 164.6, 171.1, 172.2. MALDI-TOF *m/z* 682.51[(M +Na)$^+$ calcd for $C_{37}H_{45}N_3NaO_8^+$ 682.31].

Example 17



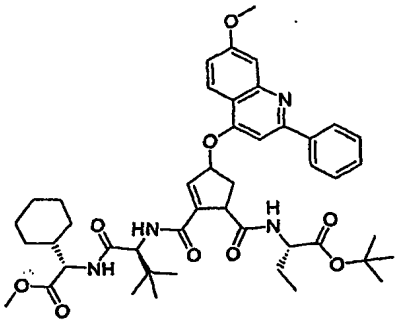
(*S*)-2-{[((1*R*,4*R*) & (1*S*,4*S*))-2-{(*S*)-1-[(2,5-Dimethoxy-phenyl)-ethyl-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid *tert*-butyl ester (17)

Compound 17 (28.6 mg, 59 %) was prepared from 12 (33 mg, 60 mmol) according to the method for the preparation of 14 using 2-amino-N-(2,5-dimethoxy-phenyl)-N-ethyl-3-methyl butyramide instead of (2-amino-3-methyl-butyrylamino)-cyclohexyl acetic acid methyl ester. This gave the title compound as a white powder.

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.75-0.95 (m, 9H) 1.05-1.18 (m, 3H), [(1.42 & 1.44) s, 9H],1.60-1.95 (m, 3H), 2.20-2.40 (m, 1H), 3.20-3.34 (m, 1H), 3.60-3.80 (m, 2H),

[3.62-3.65 (m, 3H)], [3.79-3.82 (m, 3H)], 3.98 (s, 3H), 4.02-4-18 (m, 1H), 4.30-4.44 (m, 2H), 6.05-6.18 (m, 1H), 6.60-6.63 (m, 1H), 6.77-6.80 (m, 2H), 6.85-6.93 (m, 2H), 7.12-7.20 (m, 2H), 7.35-7.60 (m, 5H), 8.02-8.20 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta$ [9.6 & 9.7], [12.5 & 12.8 ], [17.1 & 17.5], [19.4 & 19.5], 25.6, [28.0 & 28.1], 32.4, 35.8, 43.0, 44.3, [50.2 & 50.3], 54.3, [54.8 & 55.0 & 55.2 & 55.5], [55.6 & 55.7 & 55.9 & 56.0], 81.7, 82.8, 98.4, 106.9, [112.4 & 112.5],113.7, 115.0, 115.2, 115.9, 116.3, 118.4, [123.0 & 123.1], [127.7 & 127.8 ], 128.8, 128.9, 129.5, 130.1, [134.1 & 134.2], 142.6, 149.1, 149.4, 153.4, 158.9,[161.4 & 161.6], [163.2 & 163.5], 170.9, [171.3 & 171.5], 172.3. MALDI-TOF *m/z* 831.62 [(M +Na)$^+$ calcd for $C_{46}H_{56}N_4NaO_9^+$ 831.39].

Example 18

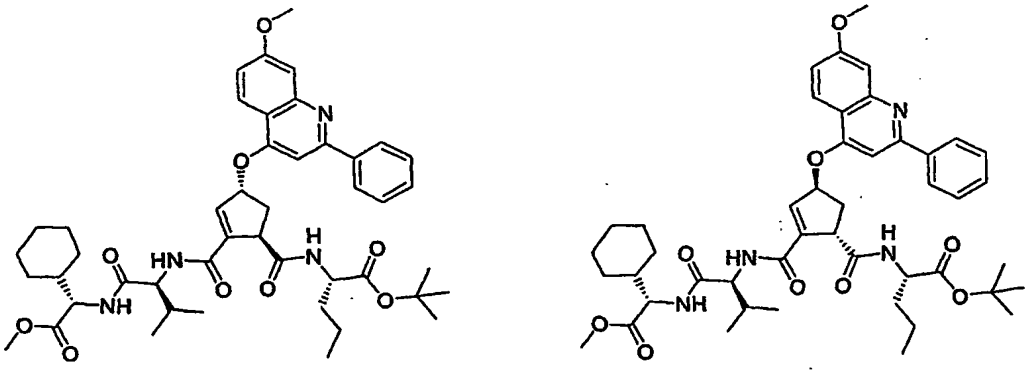


(*S*)-2-{[((1*R*,4*R*) &(1*S*,4*S*))-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid *tert*-butyl ester (18)

Compound 18 (16.1 mg, 26 %) was prepared from 12 (43.2 mg, 0.077 mmol) according to the method for the preparation of 14 using (2-amino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester instead of (2-amino-3-methyl-butyrylamino)-cyclohexyl acetic acid methyl ester. Flash column chromatography was performed in toluene/ethyl acetate 3:1 instead of 6:1: This gave the title compound as a white powder.

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.77-0.83 (m, 3H), [(0.92 & 0.93) s, 9H] 0.94-1.20 (m, 4 H), [(1.36 & 1.38) s, 9H], 1.42-1.76 (m, 8H), 2.20-2.38 (m, 1H), 2.81-2.96 (m, 1H), 3.20-3.22 (m, 1H), 2.78 (s, 3H), [(3.83 & 3.85) s, 3H], 3.97-4.02 (m, 1H), 4.17-4.21 (m, 1H), 4.22-4.37 (m, 2H), 5.85-5.97 (m, 1H), [6.76-6.78 (m, 0.5H)], [6.80-6.82 (m, 0.5H)], 6.98-7.05 (m, 3H), 7.23-7.41 (m, 6H), 7.82-7.99 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta$ [9.4 & 9.5 ], [25.4 & 25.5], 25.8, [26.5 & 26.6], [27.9 & 28.0], [28.4 & 28.5], 29.3, [35.4 & 35.7], [36.0 & 36.4], [40.5 & 40.7], [50.2 & 50.5], [52.1 & 52.2],[54.1 & 54.3], 55.5, [57.0 & 57.3], [60.4 & 60.7], [81.8 & 82.0], [82.4 & 82.5] 98.1, 107.5, 115.0, 118.1, 123.0, 127.5, 128.7, 128.8, 129.2, 134.9, 135.8, 141.9, 142.5, 151.3, 159.4, [160.9 & 161.3 ], [163.7 & 163.9], [169.9 & 170.0] [170.0 & 171.3], [172.5 & 172.4]. MALDI-TOF *m/z* 835.68 [(M +Na)$^+$ calcd for $C_{46}H_{60}N_4NaO_9^+$ 835.43].

Example 19



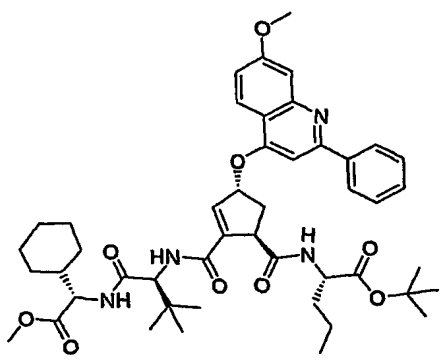
(*S*)-2-{[(1*R*,4*R*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (19a) and (*S*)-2-{[(1*S*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (19b)

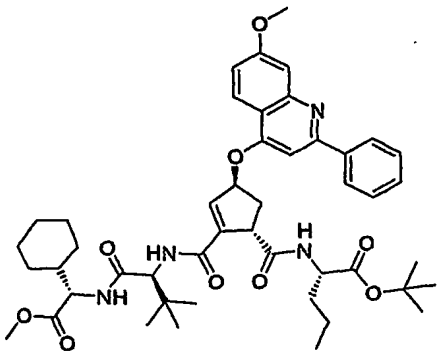
The acid 11 (0.051 g, 0.087 mmol) and (2-amino-3-methyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (0.054 g, 0.21 mmol) were dissolved in DMF (1.5 mL) and

cooled in an ice-bath. DIPEA (16 mg, 0.12 mmol) and HATU (47 mg, 0.13 mmol) were added. After two and a half hours the mixture was co-concentrated with toluene and methanol and then purified by flash column chromatography (toluene/ethyl acetate 3:1). Further purification was performed on HPLC (90 % MeOH + 0.2 % TEA). This gave after co-concentration the two diastereomers 19a (9.4 mg, 13 %) and 19b (5.3 mg, 7 %) as slightly yellow syrups. After lyophilisation 19a and 19b were collected as white powders:

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.86-0.93 (m, 3H), 0.94-1.00 (m, 6H), 1.00-1.41 (m, 7H), 1.46 (s, 9H), 1.50-1.88 (m, 8H), 2.05-2.20 (m, 1H), 2.20-2.37 (m, 1H), 3.12-3.25 (m, 1H), 3.73 (s, 3H), 3.97 (s, 3H), 4.05-4.20 (m, 1H), 4.40-4.55 (m, 3H), 6.02-6.18 (m, 1H), 6.30 (d, $J$ = 8.52 Hz, 1H), 6.63 (s, 1H), 6.76 (d, $J$ = 8.51 Hz, 1H), 7.06-7.16 (m, 2H), 7.42-7.56 (m, 5H), 8.00-8.12 (m, 3H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 14.0, 18.4, 19.3, 26.1, 28.3, 28.5, 29.7, 31.9, 34.9, 36.0, 41.0, 50.7, 52.4, 53.3, 55.7, 57.2, 58.6, 82.0, 82.7, 98.4, 105.7, 107.7, 115.2, 118.4, 123.2, 125.3, 127.9, 129.0, 129.1, 135.1, 138.0, 142.4, 151.6, 159.4, 161.6, 164.3, 170.7, 171.2, 172.3. 19b: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.90-1.04 (m, 9H), 1.04-1.43 (m, 7H), 1.47 (s, 9H), 1.50-1.87 (m, 8H), 2.10-2.27 (m, 1H), 2.33-2.45 (m, 1H), 3.10-3.20 (m, 1H), 3.73 (s, 3H), 3.96 (s, 3H), 4.02-4.10 (m, 1H), 4.36-4.53 (m, 3H), 6.00-6.16 (m, 1H), 6.30 (d, $J$ = 8.52 Hz, 1H), 6.73 (s, 1H), 6.86 (d, $J$ = 7.96 Hz, 1H), 7.08-7.16 (m, 2H), 7.36-7.56 (m, 5H), 8.03-8.11 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 14.0, 18.6, 19.2, 26.1, 28.2, 28.7, 29.7, 34.5, 36.1, 36.6, 40.8, 50.5, 52.4, 53.4, 55.7, 57.3, 59.1, 64.8, 82.3, 98.4, 105.8, 107.8, 115.3, 118.4, 123.2, 127.8, 129.0, 129.4, 135.2, 142.2, 144.9, 151.0, 151.6, 159.2, 164.3, 164.3, 170.2, 171.6, 171.9

Example 20





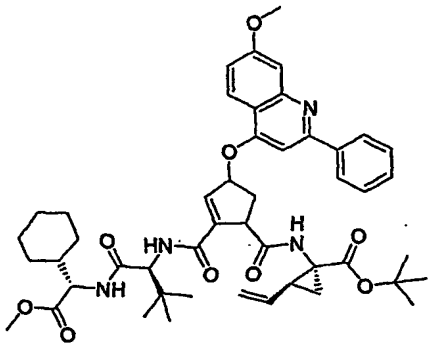
(*S*)-2-{[(1*R*,4*R*)-2-{(*R*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (20a) and
(*S*)-2-{[(1*S*,4*S*)-2-{(*R*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (20b)

Method A: The carboxylic acid 11 (57 mg, 0.10 mmol) was dissolved in warm (50 °C) dry THF (2 mL). (2-Amino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (50 mg, 0.12 mmol), DIPEA (30 mg, 0.23 mmol), DCC (25 mg, 0.12 mmol) and HOBt (17 mg, 13 mmol) were added. After two hours the mixture was concentrated and added to a short column (toluene/Ethyl acetate 1:3 + 3 % AcOH). Then it was further purified on HPLC using 90 % MeOH + 0.2 % TEA. The diastereomeric products were not separated. After HPLC the solution was co-concentrated with toluene and methanol to give 20 (28 mg, 34%).

Method B: To an ice-cold solution of 11 (60 mg, 0.10 mmol) and (2-amino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (42 mg, 0.15 mmol) DIPEA (19 mg, 0.15 mmol) and HATU (62 mg, 0.16 mmol) were added. After two and a half hours the mixture was concentrated and purified using column chromatography. (toluene/Ethyl acetate 3:1). The diastereomeric mixture was separated using HPLC (90 % MeOH + 0.2 % TEA). This gave 20a (6 mg, 6 %) and 20b (9 mg, 10%).

20a: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.82-0.90 (m, 3H), 1.01 (s, 9H), 1.05-1.40 (m, 7H), 1.46 (s, 9H), 1.50-1.80 (m, 8H), 2.20-2.35 (m, 1H), 3.07-3.25 (m, 1H), 3.73 (s, 3H), 3.97 (s, 3H), 4.11 (d, $J$ = 7.96 Hz, 1H), 4.38-4.52 (m, 3H), 6.03-6.12 (m, 1H), 6.24 (d, $J$ = 8.79 Hz, 1H), 6.63 (s, 1H), 6.82 (d, $J$ = 9.06 Hz, 1H), 7.07-7.27 (m, 2H), 7.36 (d, $J$ = 7.96 Hz, 1H), 7.41-7.55 (m, 4H), 8.01-8.10 (m, 3H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 14.0, 18.8, 26.1, 26.8, 28.2, 28.6, 29.6, 34.9, 35.6, 36.2, 40.9, 50.7, 52.4, 53.3, 55.7, 57.3, 60.8, 82.0, 82.7, 98.4, 105.2, 107.7, 115.2, 118.4, 123.2, 127.9, 129.0, 129.4, 131.1, 135.1, 138.4, 142.4, 153.3, 159.6, 161.6, 164.2, 170.1, 171.3, 172.2. 20b: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 0.90-0.98 (m, 3H), 1.04 (s, 9H), 1.08-1.40 (m, 7H), 1.44 (s, 9H), 1.55-1.90 (m, 8H), 2.20-2.38 (m, 1H), 3.10-3.22 (m, 1H), 3.73 (s, 3H), 3.97 (s, 3H), 4.02-4.15 (m, 1H), 4.35-4.48 (m, 3H), 6.00-6.08 (m, 1H), 6.72 (s, 1H), 6.90 (d, $J$ = 9.06 Hz, 1H), 7.09-7.20 (m, 3H), 7.44-7.55 (m, 5H), 8.03-8.11 (m, 3H).

Example 21



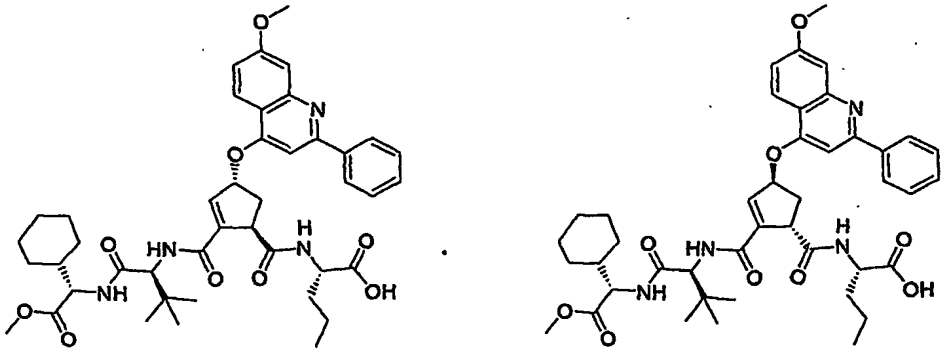
(1*R*,2*S*)-1-{[((1*R*,4*R*) & (1*S*,4*S*))-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid *tert*-butyl ester (21)

The acid 13 (35 mg, 0.060 mmol) and (2-amino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (22 mg, 0.080 mmol) were dissolved in dry THF

(1.5 mL) and warmed to 50 °C. HOBt (11 mg, 0.080 mmol) and DCC (31 mg, 0.15 mmol) were added. After one hour the mixture was co-concentrated with toluene and methanol and then purified by flash column chromatography (toluene/ethyl acetate 1:1). Further purification was performed on HPLC (80 % MeOH + 0.2 % TEA. The diastereomeric mixture 21 was concentrated and gave a slightly yellow oil (26.4 mg, 53 %). After lyophilisation 21 was collected as a white powder.

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ [(0.98 & 1.00), s, 9H], 1.01-1.38 (m, 5H), [(1.39 & 1.40) s, 9H], 1.52-1.63 (m, 4H), 1.65-1.80 (m, 4H), 1.90-2.05 (m, 1H), 2.20-2.40 (m, 1H), 3.02-3.20 (m, 1H), [(3.66 & 3.67) s, 3H), 3.98 (s, 3H), 3.99-4.02 (m, 1H), 4.30-4.45 (m, 2H), 5.05-5.11 (m, 1H), 5.20-5.30 (m, 1H), 5.60-5.81 (m, 1H), 6.03-6.17 (m, 1H), 6.77-6.82 (m, 1H), 6.95-7.22 (m, 5H), 7.40-7.50 (m, 4H), 8.01-8.10 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta$ 22.3, [25.7 & 25.8], [26.4 & 26.5], [28.0 & 28.4] 29.2, 32.7, 33.3, [35.3 & 35.4], 36.0, [40.2 & 40.3], 40.7, 52.0, 55.4, [57.2 & 57.4] [60.4 & 60.5], [87.6 & 87.7], [82.3 & 82.5], 98.4, 107.0, 114.9, [117.4 & 117.5], 118.1, 122.9, 127.6, 128.6,128.9, 129.2, [133.6 & 133.8], 135.9, 136.9, 140.1, [141.4 & 141.6], 151.1, 159.6, [160.9 & 161.3], [164.2 & 164.6], 168.9, 170.3, [172.1 & 172.6]. MALDI-TOF *m/z* 859.77 [(M +Na)$^+$ calcd for $C_{48}H_{60}N_4NaO_9^+$ 859.43].

Example 22



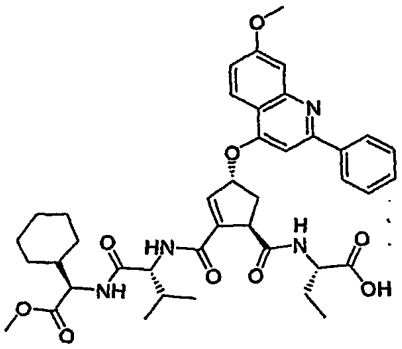
(*S*)-2-{[(1*R*,4*R*)-2-{(*R*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid (22a) and

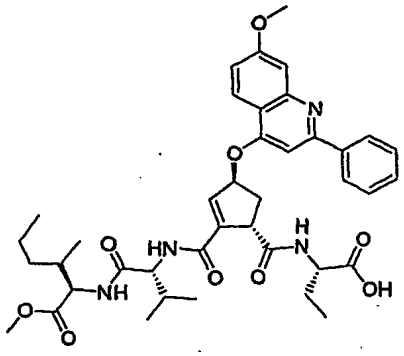
(*S*)-2-{[(1*S*,4*S*)-2-{(*R*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid (22b)

The tert.butyl ester 20 (28 mg, 0.034 mmol), TES (8.7 mg, 0.075 mmol), DCM (1 mL) and TFA (1 mL) were mixed in a round bottomed flask. Two hours later the mixture was concentrated and the diastereomers were separated on HPLC using 65 % MeOH + 0.2 % TEA as mobile phase. This gave 22a (15 mg, 55 %) and 22b (12 mg, 45 %) as slightly yellow syrups. After lyophilisation the title compounds were collected as white powders.

22a: $[\alpha]^{22}D$ + 155.8; $^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 0.90-0.97 (m, 3H), 1.03 (s, 9H), 1.05-1.50 (m, 7H), 1.50-1.80 (m, 8H), 2.43-2.55 (m, 1H), 2.77-2.90 (m, 1H), 3.68 (s, 3H), 3.96 (s, 3H), 4.20-4.30 (m, 2H), 4.31-4.40 (m, 1H), 4.45-4.50 (m, 1H), 6.03-6.11 (m, 1H), 6.98 (s, 1H), 7.12-7.19 (m, 1H), 7.36 (s, 1H), 7.41 (d, $J$ = 2.2 Hz, 1H), 7.50-7.60 (m, 3H), 8.03-8.10 (m, 3H): $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 13.1, 19.1, 26.1, 28.7, 28.9, 29.5, 34.3, 34.8, 35.9, 40.1, 50.8, 51.2, 54.8, 55.0, 57.9, 60.7, 83.5, 99.1, 106.0, 115.2, 118.2, 123.3, 127.8, 128.0, 128.7, 128.8, 129.7, 135.2, 139.8, 143.7, 150.6, 160.1, 162.2, 165.2, 171.7, 172.2, 173.4. 22b: $[\alpha]^{22}D$ -72,3; $^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 0.90-0.97 (m, 3H), 1.02 (s, 9H), 1.07-1.35 (m, 7H), 1.53-1.90 (m, 8H), 2.46-2.61 (m, 1H), 2.76-2.88 (m, 1H), 3.69 (s, 3H), 3.96 (s, 3H), 4.15-4.35 (m, 2H), 4.37-4.41 (m, 1H), 4.42-4.47 (m, 1H), 6.02-6.12 (m, 1H), 7.02 (s, 1H), 7.16 (dd, $J$ = 2.47, 9.34 Hz, 1H), 7.32 (s, 1H), 7.40 (d, $J$ = 2.47 Hz, 1H), 7.48-7.58 (m, 3H), 8.03-8.12 (m, 3H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 13.0, 18.8, 25.9, 26.0, 28.8, 29.4, 34.2, 34.8, 36.3, 39.9, 48.8, 50.5, 51.1, 54.8, 57.9, 60.5, 82.8, 99.0, 106.0, 115.1, 118.2, 123.1, 127.8, 127.9, 128.7, 129.0, 129.5, 136.7, 139.8, 142.8, 150.6, 160.1, 162.0, 162.2, 164.7, 172.1, 173.5.

Example 23



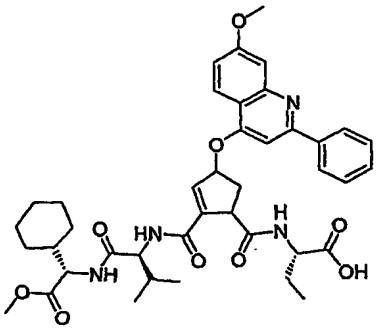


(*S*)-2-{[(1*R*,4*R*)-2-{(*R*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid (23a) and (*S*)-2-{[(1*S*,4*S*)-2-{(*R*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid (23b)

Compound 23a (6.6 mg, 50 %) and compound 23b (1.3 mg, 10 %) were prepared from 15 (14 mg, 0.018 mmol) according to the method for the preparation of 22a and 22b. This gave the title compounds as white powders.

23a: $^1$H-NMR (300 MHz, $CD_3OD$): 0.88-1.02 (m, 9H), 1.02-1.40 (m, 7H), 1.55-1.97 (m, 6H), 2.01-2.10 (m, 1H), 2.38-2.52 (m, 1H), 2.88-3.00 (m, 1H), 3.77 (s, 3H), 3.98 (s, 3H), 4.08-4.20 (m, 1H), 4.22-4.40 (m, 3H). 6.03-6.18 (m, 1H), 6.86-6.99 (m, 1H), 7.08-7.20 (m, 1H), 7.23 (s, 1H), 7.40-7.43 (m, 1H), 7.45-7.70 (m, 3H), 8.02-8.20 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 9.0, 17.6, 18.2, 24.5, 25.3, 28.1, 28.8, 30.9, 35.4, 39.4, 49.6, 51.1, 54.7, 57.2, 58.0, 82.4, 98.5, 105.5, 114.5, 117.7, 122.7, 127.2, 127.3, 128.2, 129.0, 135.6, 136.4, 141.7, 149.9, 159.5, 161.2, 161.4, 164.0, 171.0, 171.7, 172.4. 23b: $^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 0.9-1.20 (m, 9H), 1.21-1.53 (m, 7H), 1.55-1.93 (m, 6H), 2.05-2.20 (m, 1H), 2.41-2.50 (m, 1H), 2.96-3-05 (m, 1H), 3.77 (s, 3H), 4.00 (s, 3H), 4.05-4.40 (m, 4H), 6.05-6.18 (m, 1H), 6.90-6.95 (m, 1H), 7.05-7.22 (m, 2H), 7.50-7.65 (m, 4H), 8.01-8.16 (m, 3H).

Example 24

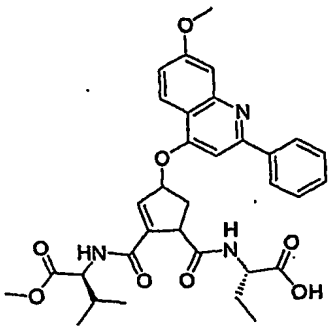


(*S*)-2-{[((1*R*,4*R*) & (1*S*,4*S*))-2-{(*S*)-1-[((*S*)-Carboxy-cyclohexyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid (24)

The tert.butyl ester 14 (13.4 mg, 0.017 mmol), TES (4.83 mg, 0.042 mmol), DCM (2 mL) and TFA (2 mL) were mixed in a round bottomed flask. One hour later the mixture was concentrated and purified by HPLC using 65 % MeOH + 0.2 % TEA as mobile phase. This gave 24 (4.3 mg, 34 %) as a slightly yellow syrup. After lyophilisation 24 was collected as a white powder.

$^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 0.91-0.99 (m, 9H), 1.00-1.28 (m, 4H), 1.55-1.78 (m, 9H), 1.92-1.95 (m, 1H), 2.00-2.05 (m, 1H), 2.93-3.01 (m, 1H), 3.75 (s, 3H), 3.97 (s, 3H), 4.10-4.40 (m, 4H), 6.05-6.15(m, 1H), 6.88-6.94 (m, 1H), 7.05-7.10 (m, 2H), 7.41-7.43 (m, 1H), 7.44-7.55 (m, 2H), 8.62-8.68 (m, 1H), 8.69-8.79 (m, 1H), 7.97-8.05 (m, 2H). $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 9.2, 18.5, 25.5, [29.0 & 29.2], [30.0 & 30.5], 35.3, 37.7, 39.7, 46.2, 50.0, [51.4 & 51.5], 53.6, 55.1, 57.1, 58.4, 83.1, 98.9, 104.9, 114.6, 118.3, 123.0, 123.4, 127.5, 128.4, 128.5, 129.7, 135.0, 142.1, 145.7, 146.2, 159.2, 161.9, 164.3, 171.5, 171.9, 172.2. MALDI-TOF *m/z* 791.27 [(M +K)$^+$ calcd for $C_{42}H_{48}KN_4O_9^+$ 791.31].

Example 25

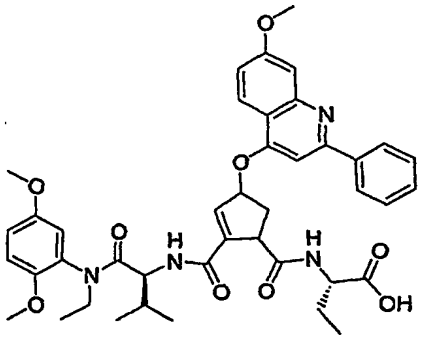


(*S*)-2-{[((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-Carboxy-propylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarbonyl]-amino}-3-methyl-butyric acid methyl ester (25)

Compound 25 (8.0 mg, 60 %) was prepared from 16 (13.8 mg, 0.022 mmol) according to the method for the preparation of 24 which gave the title compound as a white powder.

$^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 0.83-1.02 (m, 9H), 1.68-1.80 (m, 1H), 1.82-2.02 (m, 1H), 2.10-2.22 (m, 1H), 2.40-2.60 (m, 1H), 2.81-2.95 (m, 1H), 3.75 (s, 3H), 4.00 (s, 3H), 4.18-4.22 (m, 1H), 4.27-4.40 (m, 2H), 6.05-6.12 (m, 1H), 6.99-7.02 (m, 1H), 7.16-7.21 (m, 1H), 7.38 (s, 1H), 7.40-7.43 (m, 1H), 7.48-7.61 (m, 3H), 7.98-8.12 (m, 3H).

Example 26

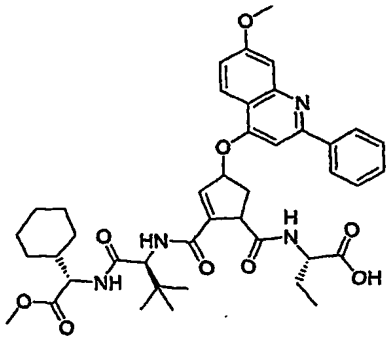


(*S*)-2-{[((1*R*,4*R*) &(1*S*,4*S*))-2-{(*S*)-1-[(2,5-Dimethoxy-phenyl)-ethyl-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid (26)

Compound 26 (5.7 mg, 36 %) was prepared from 17 (16.7 mg, 0.021 mmol) according to the method for the preparation of 24 which gave the title compound as a white powder.

$^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 0.75-0.81 (m, 6H), 0.82-0.98 (m, 3H), 1.00-1.10 (m, 3H), 1.60-2.00 (m, 3H), 2.40-2.56 (m, 1H), 2.80-2.88 (m, 1H), 3.18-3.24 (m, 1H), 3.40-3.46 (m, 1H), [3.67-3.80 (m, 6H)], 3.97 (s, 3H), 4.10-4.20 (m, 1H), 4.21-4.40 (m, 2H), 6.02-6.17(m, 1H), 6.75-6.82 (m, 1H), 6.84-7.01 (m, 3H), 7.10-7.20 (m, 1H), 7.30-7.37 (m, 1H), 7.40-7.43 (m, 1H), 7.50-7.60 (m, 3H), 8.00-8.17 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 9.6, [11.8 & 12.0], [17.2 & 17.4], 18.9, 25.0, 32.3, 35.7, 43.3, 44.2, [50.3 & 50.5], [54.5 & 54.8 & 54.9 & 55.0], [55.1 & 55.2 & 55.3 & 56.0] ,58.7, 83.6, 99.3, 105.5, [112.5 & 112.7], 114.3, [15.1 & 115.2], 115.7, 116.1, 118.4, [123.3 & 123.4], 125.2, [128.0 & 128.1, 128.8, 129.1, 129.8, [135.1 & 135.3], 139.2, [143.3 & 144.4], 149.2, [149.6 & 149.9], 153.8, 159.9, 162.4, [163.9 & 164.5], 172.1, 172.8, [173.6 & 173.7]. MALDI-TOF *m/z* 775.30 [(M +Na)$^+$ calcd for $C_{42}H_{48}N_4NaO_9^+$ 775.33].

Example 27

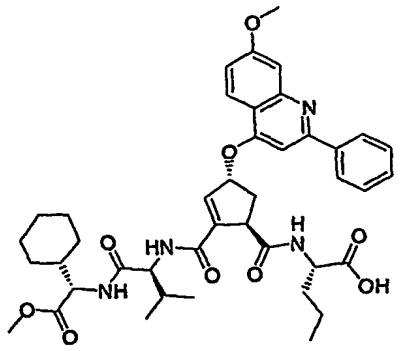


(*S*)-2-{[((1*R*,4*R*) &(1*S*,4*S*))-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid (27)

Compound 27 (6.0 mg, 72 %) was prepared from 18 (8.6 mg, 0.011 mmol) according to the method for the preparation of 24. Purification by HPLC (60 % methanol + 0.2 % TEA) gave the title compound as a white powder.

$^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 0.88-0.95 (m, 3H), 0.96 (s, 9H), 0.97-1.24 (m, 4H), 1.57-1.62 (m, 3H), 1.58-1.78 (m, 4H), 1.79-1.99 (m, 1H), 2.35-2.44 (m, 2H), 2.85-2.98 (m, 1H), [(3.67 & 3.69) s, 3H], 3.94 (s, 3H), 4.10-4.20 (m, 1H), 4.30-4.40 (m, 3H), 6.00-6.09 (m, 1H), [6.80-6.82 (m, 0.5H)] [6.85-6.87 (m, 0.5H)], 7.05-7.19 (m, 2H), 7.38-7.55 (m, 4H), 7.95-8.07 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ [9.1 & 9.2], [24.7 & 24.9], [25.4 & 25.5], [25.9 & 26.0 ], [28.3 & 28.4], 28.9, [34.8 & 34.9], [35.6 & 35.9], [39.6 & 39.7], [49.9 & 50.1], [51.4 & 51.2], [53.9 & 54.0] 55.0, [57.2 & 57.4], 60.0, [82.1 & 82.5], 98.6, 106.2, 114.7, 117.8, 122.7, 127.5, 127.7, [128.4 & 128.5], 129.1, 135.3, 136.3, 141.6, 142.0, 150.5, 159.8, [161.0 & 161.3] [164.0 & 164.1], [171.6 & 171.9], [172.2 & 172.3], [173,0 & 173.2].MALDI-TOF *m/z* 779.43 [(M +Na)$^+$ calcd for $C_{42}H_{52}N_4NaO_9^+$ 779.36].

Example 28

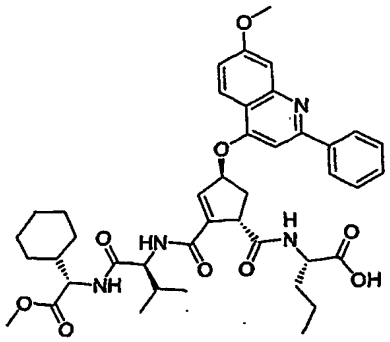


(*S*)-2-{[(1*R*,4*R*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (28)

The tert.butyl ester 19a (7.6 mg, 0.0094 mmol) and TES (2.4 mg, 0.021 mmol) were dissolved in DCM (1 mL) and the mixture was cooled in an ice-bath. TFA (1 mL) was added. After two hours the mixture was concentrated and purified on HPLC using 60 % MeOH + 0.2 % TEA as mobile phase. This gave 28 (6.1 mg, 86 %) as a slightly yellow syrup. After lyophilisation the title compound was collected as white powder.

$^1$H-NMR (300 MHz, $CD_3OD$ + CDCl3 (1:1)): $\delta$ 0.90-1.00 (m, 9H), 1.00-1.30 (m, 7H), 1.50-1.90 (m, 8H), 2.00-2.10 (m, 1H), 2.40-2.50 (m, 1H), 2.85-2.98 (m, 1H), 3.65-3.72 (s, 3H), 3.99 (s, 3H), 4.15-4.22 (m, 1H), 4.24-4.35 (m, 2H), 4.38-4.44 (m, 1H), 6.10-6.20 (m, 1H), 6.95-6.96 (m, 1H), 7.16-7.23 (m, 1H), 7.31 (s, 1H), 7.42 (d, $J$ = 2.47 Hz, 1H), 7.53-7.72 (m, 3H), 7.97-8.16 (m, 3H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$ + $CDCl_3$ 1:1): $\delta$ 13.5, 18.3, 19.0, 26.0, 29.0, 29.7, 31.0, 34.1, 35.8, 40.2, 51.9, 55.9, 57.7, 58.9, 63.5, 68.4, 84.0, 99.6, 104.8, 105.7, 115.1, 119.0, 123.7, 128.1, 128.9, 129.1, 130.4, 131.3, 135.3, 138.0, 142.9, 159.5, 162.8, 164.8, 172.2, 172.2, 172.4

Example 29

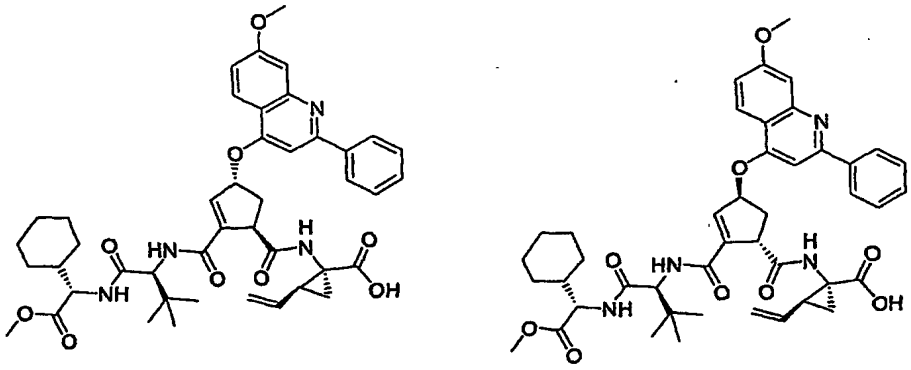



(*S*)-2-{[(1*S*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (29)

Compound 29 (1.3 mg, 26 %) was prepared from 19b (5.3 mg, 0.065 mmol) according to the method for the preparation of 28. This gave the title compound as a white powder.

$^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 0.85-1.00 (m, 9H), 1.00-1.23 (m, 7H), 1.50-1.78 (m, 8H), 2.05-2.23 (m, 1H), 2.50-2.66 (m, 1H), 2.70-2.85 (m, 1H), 3.69 (s, 3H), 3.92 (s, 3H), 4.02-4.16 (m, 1H), 4.20-4.25 (m, 1H), 4.35-4.40 (m, 2H), 6.09 (m, 1H), 7.00 (s, 1H), 7.12-7.18 (dd, $J$ = 2.47, 2.19 Hz, 1H), 7.30 (s, 1H), 7.40 (d, $J$ = 2.42 Hz, 1H), 7.48-7.74 (m, 3H), 8.03-8.10 (m, 3H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta$ 11.7, 16.5, 17.0, 24.4, 27.2, 27.9, 29.0, 29.1 37.5, 41.8, 49.7, 50.5, 53.3, 56.3, 63.5, 66.5, 81.0, 100.3, 101.0, 105.7, 113.6, 121.6, 126.3, 127.1, 127.9, 130.1, 131.4, 135.6, 138.7, 141.1, 150.4, 160.2, 160.5, 165.3, 173.0, 173.6, 173.7

Example 30

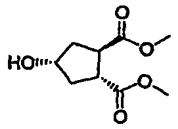


(1*R*,2*S*)-1-{[(1*R*,4*R*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (30a) and
1*R*,2*S*)-1-{[(1*S*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-2-vinyl-cyclopropane-carboxylic acid (30b)

Compound 30a (6.3 mg, 49 %) and compound 30b (5.6 mg, 43 %) were synthesized from 21 (13.8 mg, 0.0016 mmol) according to the method of the preparation of 22a and 22b. 30a and 30b: White powder.

30a: $^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 1.02 (s, 9H), 1.03-1.43 (m, 5H), 1.61-1.95 (m, 8H), 2.11-2.21 (m, 1H), 2.43-2.58 (m, 1H), 2.97-3.04 (m, 1H), 3,78 (s, 3H), 4.01 (s, 3H), 4.02-4.17 (m, 1H), 4.25-4.40 (m, 2H), 5.10-5-20 (m, 1H), 5.27-5.40 (m, 1H), 6.77-6.94 (m, 1H), 6.10-6.20 (m, 1H), 6.97 (s, 1H), 7.18 (dd, $J$ = 2.5, 9.2 Hz, 1H), 7.22 (s, 1H), 7.46 (d, $J$ = 2.5 Hz, 1H), 7.52-7.65 (m, 3H), 8.00-8.18 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 13.5, 25.3, 25.7, 28.3, 28.7, 29.0, 32.8, 34.6, 35.3, 39.3, 49.7, 51.1, 54.6, 57.2, 59.8, 82.1, 98.4, 105.8, 114.5, 116.3, 117.6, 122.6, 127.2, 128.1, 128.2, 128.8, 130.2, 133.7, 136.0, 139.5, 141.5, 150.3, 159.7, 161.0, 161.2, 163,4, 171.6, 172.5. MALDI-TOF $m/z$ 803.56 [(M +Na)$^+$ calcd for $C_{44}H_{52}N_4NaO_9^+$ 803.36]. 30b: $^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 1.03 (s, 9H), 1.04-1.42 (m, 5H), 2.60-2.90 (m, 8H), 2.17-2.22 (m, 1H), 2.40-2.55 (m, 1H), 2.96-3.10 (m, 1H), 3.77 (s, 3H), 4.01 (s, 3H), 4.05-4.16 (m, 1H), 4.30-4.40 (m, 2H), 5.15-5.20 (m, 1H), 5.25-5.40 (m, 1H), 5.78-5.95 (m, 1H), 6.10-6.20 (m, 1H), 6.98 (s, 1H), 7.17 (dd, $J$ = 2.5, 9.1 Hz, 1H), 7.26 (s, 1H), 7.46 (d, $J$ = 2.5 Hz, 1H), 7.50-7.65 (m, 3H), 8.03-8.28 (m, 3H). $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 13.7, 26.0, 26.3, 28.8, 29.4, 29.6, 34.0, 35.2, 35.8, 40.1, 50.6, 51.7, 55.3, 57.8, 60.6, 83.0, 99.1, 106.3, 115.2, 117.0, 118.3, 123.2, 127.9, 128.0, 128.8, 129.6, 130.6, 134.4, 136.1, 140.0, 142.5, 150.8, 160.3, 161.8, 162.0, 165.7, 172.3, 173.0

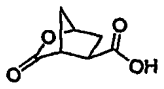
Example 31




*trans*-(3*R*,4*R*)-Bis(methoxycarbonyl)cyclopentanol (31)

Sodium borohydride (1.11 g, 0.029 mol) was added to a stirred solution of (1R, 2S)-4-oxo-cyclopentane1,2-dicarboxylic acid dimethyl ester (4.88 g, 0.0244 mol) in methanol (300 mL) at 0 °C. After 1 h the reaction was quenched with 90 mL brine, concentrated and extracted with ethyl acetate. The organic phases were pooled, dried, filtered and concentrated. The crude product was purified by flash column chromatography (toluene/ethyl acetate 1:1) to give 31 (3.73 g, 76%) as a yellow oil.

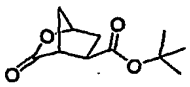
Example 32



3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid (32)

Sodium hydroxide (1M, 74 mL, 0.074 mol) was added to a stirred solution of 31 (3.73 g, 0.018 mol) in methanol (105 mL) at room temperature. After 4 h, the reaction mixture was neutralized with 3M HCl, evaporated and co-evaporated with toluene several times. Pyridine (75 mL) and $Ac_2O$ (53 mL) were added and the reaction mixture was allowed to shake overnight at room temperature. The mixture was then co-evaporated with toluene and purified by flash column chromatography (ethyl acetate + 1% acetic acid) to give 32 (2.51 g, 88%) as a yellow oil.

Example 33



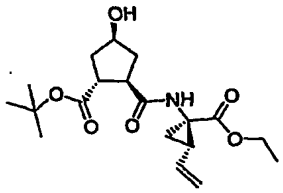
3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid *tert*-butyl ester (33)

DMAP (14 mg, 0.115 mmol) and $Boc_2O$ (252 mg, 1.44 mmol) was added to a stirred solution of 32 (180 mg, 1.15 mmol) in 2 mL $CH_2Cl_2$ under inert argon atmosphere at 0 °C. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was concentrated and the crude product was purified

by flash column chromatography (toluene/ethyl acetate gradient 15:1, 9:1, 6:1, 4:1, 2:1) to give 33 (124 mg, 51%) as white crystals.

$^1$H-NMR (300 MHz, $CD_3OD$) δ 1.45 (s, 9H), 1.90 (d, $J$ = 11.0 Hz, 1H), 2.10-2.19 (m, 3H), 2.76-2.83 (m, 1H), 3.10 (s, 1H), 4.99 (s, 1H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$) δ 27.1, 33.0, 37.7, 40.8, 46.1, 81.1, 81.6, 172.0, 177.7.

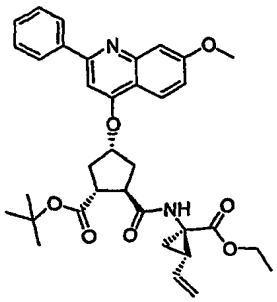
Example 34




(1*R*,2*R*,4*S*)-2-((1*R*,2*S*)-1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-cyclopentanecarboxylic acid *tert*-butyl ester (34)

Compound 33 (56 mg, 0.264 mmol) was dissolved in dioxane/ water 1:1 (5 mL) and the mixture was cooled to 0 °C. 1 M lithium hydroxide (0.52 mL, 0.520 mmol) was added and the mixture was stirred at 0 °C for 45 minutes, after which the mixture was neutralized with 1M hydrochloric acid and evaporated and coevaporated with toluene. The residue was dissolved in DMF (5 mL) and (1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride (60 mg, 0.313 mmol) and diisopropylethylamine (DIEA) (138 µL, 0.792 mmol) were added and the solution was cooled to 0 °C. HATU (120 mg, 0.316 mmol) was added and the mixture was stirred for 0.5 h at 0 °C and for an additional 2 h at room temperature. The mixture was then evaporated and extracted with EtOAc, washed with brine, dried, filtered and concentrated. Purification by flash column chromatography (toluene/ EtOAc 1:1) provided compound 34 (86 mg, 89 %) as a colorless oil.

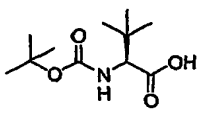
Example 35



(1*R*,2*R*,4*R*)-2-((1*R*,2*S*)-1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid *tert*-butyl ester (35)

Compound 34 (73 mg, 0.199 mmol) was dissolved in dry THF (4 mL) and 2-phenyl-7-methoxy-4-quinolinol (86 mg, 0.342 mmol) and triphenylphosphine (141 mg, 0.538 mmol) were added. The mixture was cooled to 0°C and DIAD (0.567 mmol) dissolved in 1 mL THF was added dropwise. The mixture was stirred for 48 h at room temperature. The solvent was evaporated and the crude product was purified by flash column chromatography gradient elution (toluene/ EtOAc 9:1, 6:1, 4:1) to give compound 35 (81 mg, 68 %).

Example 36



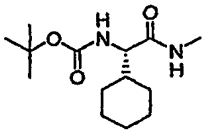
Boc-L-*tert*-leucine-OH (36)

Triethylamine (890 µL, 6.40 mmol) was added dropwise to a stirred solution of L-*tert*-leucine (300 mg, 2.29 mmol) and di-*tert*-butyl dicarbonate (599 mg, 2.74 mmol) in dioxane/ water 1:1 (8 mL) and the solution was stirred overnight. The mixture was extracted with petroleum ether (2×) and the aqueous phase was cooled to 0 °C and carefully acidified to pH 3 by slow addition of 4M $NaHSO_4 \cdot H_2O$. The acidified water phase was extracted with EtOAc (3×) and the combined organic phases were washed with brine (2×) and was then dried, filtered and concentrated to give

compound 36 (522 mg, 99 %) as a colorless powder. No further purification was needed.

$^1$H-NMR (300 MHz, $CD_3OD$) δ 0.99 (s, 9H), 1.44 (s, 9H), 3.96 (s, 1H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$) δ 27.1, 28.7, 34.9, 68.0, 80.5, 157.8, 174.7.

Example 37

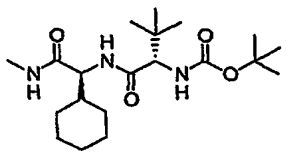


((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamic acid *tert*-butyl ester (37)

Boc-Chg-OH (387 mg, 1.50 mmol) was coupled to methylamine hydrochloride (111 mg, 1.65 mmol) using the same HATU coupling conditions as in the synthesis of compound 34. The crude product was extracted with EtOAc, washed with brine and concentrated. Purification by flash column chromatography (EtOAc) provided compound 37 (307 mg, 76 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 0.91-1.13 (m, 2H), 1.14-1.31 (m, 3H), 1.44 (s, 9H), 1.61-1.80 (m, 6H), 2.80 (d, $J$ = 4.7 Hz, 3H), 3.91 (dd, $J$ = 7.1, 9.1 Hz, 1H), 5.23 (b, 1H), 6.52 (bs, 1H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$) δ 25.9, 26.0, 26.1, 28.3, 28.5, 29.6, 40.5, 59.5, 79.7, 155.9, 172.4.

Example 38

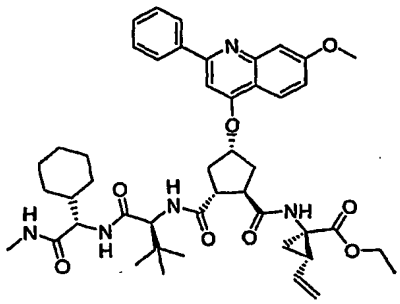


{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester (38)

To a solution of compound 37 (98 mg, 0.362 mmol) in methylene chloride (3 mL) were added triethylsilane (115 mL, 0.742 mmol) and TFA (3 mL). The mixture was stirred for 2 h at room temperature and was then evaporated and coevaporated with toluene. The deprotected amine was dissolved in DMF (5 mL) and coupled to compound 36 (84 mg, 0.363 mmol) using the same HATU coupling conditions as in the synthesis of 34. The crude product was extracted with EtOAc, washed with brine, dried, filtered and concentrated. Purification by flash column chromatography (toluene/ EtOAc 1:1) provided compound 38 (128 mg, 92 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.02-1.30 (m, 5H), 1.44 (s, 9H), 1.58-1.77 (m, 4H), 1.78-1.89 (m, 2H), 2.79 (d, *J* = 4.7 Hz, 3H), 4.11 (d, *J* = 9.3 Hz, 1H), 4.33 (app. t, *J* = 8.5 Hz, 1H), 5.65 (b, 1H), 7.25 (b, 1H), 7.39 (b, 1H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$) δ 25.9, 25.9, 26.0, 26.2, 26.8, 28.4, 29.0, 29.7, 34.5, 39.7, 58.4, 62.4, 79.4, 156.0, 171.4, 171.8.

Example 39



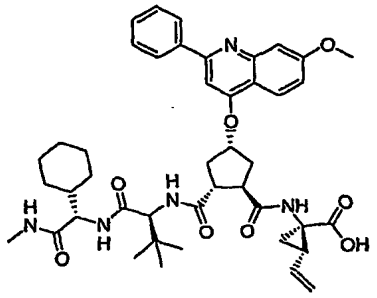
(1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (39)

To a solution of compound 35 (30 mg, 0.050 mmol) in methylene chloride (1.5 mL) were added triethylsilane (21 µL, 0.132 mmol) and TFA (1.5 mL). The mixture was stirred for 2 h at room temperature and was then evaporated and coevaporated with toluene. The amine 38 (1.3 eq) was deprotected in the same manner as compound 35 and was then coupled to deprotected compound 35 using the same HATU coupling conditions as in the synthesis of 34. The crude product was extracted with EtOAc, washed with brine, dried, filtered and concentrated. Purification using HPLC (MeOH/ water 9:1 + 0.2% triethylamine) provided compound 39 (30 mg, 74%) as a colorless solid.

$^1$H-NMR (300 MHz, $CD_3OD$) δ 0.81-1.14 (m, 4H), 0.99 (s, overlapped, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.35-1.51 (m, 4H), 1.52-1.65 (m, 3H), 1.66-1.72 (m, 2H), 2.03-2.20 (m, 2H), 2.24-2.39 (m, 1H), 2.46-2.56 (m, 1H), 2.66 (s, 3H), 2.72-2.85 (m, 1H), 3.39-3.48 (m, 2H), 3.90 (s, 3H), 4.03-4.15 (m, 3H), 4.44 (s, 1H), 5.09 (dd, *J* = 1.9, 10.3 Hz, 1H), 5.19-5.27 (m, 1H), 5.25 (dd, overlapped, 1H), 5.79 (ddd, *J* = 8.8, 10.3, 17.2 Hz, 1H), 6.99 (s, 1H), 7.07 (dd, *J* = 2.5, 9.1, Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.43-7.52 (m, 3H), 7.86-7.98 (m, 2H), 8.05 (d, *J* = 9.3 Hz, 1H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$) δ 14.7, 23.4, 26.0, 26.9, 27.1, 27.3, 30.1, 30.7, 35.0, 35.4, 38.3, 38.8, 40.9, 41.0, 47.9, 55.9, 59.6, 62.0, 62.4, 79.8, 99.9, 107.3, 116.4, 118.0, 119.1, 124.4, 128.9, 129.8, 130.5, 135.3, 141.3, 152.1, 161.1, 162.4, 163.0, 171.6, 172.5, 173.7, 175.2, 176.8.

Maldi-TOF-spectrum: $(M+H)^+$ calcd: 810.4, found: 810.5; $(M+Na)^+$ calcd: 832.4, found: 832.4; $(M+K)^+$ calcd: 848.5, found: 848.4.

Example 40



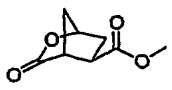
(1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (40)

To a solution of compound 39 (20 mg, 0.025 mmol) in THF/MeOH/water 2:1:1 (2 mL) at 0 °C was added 1M LiOH (175 µL, 0.175 mmol) and the solution was allowed to attain room temperature and was stirred for 48 h. The solution was acidified to pH 3 with 1M HCl and was then evaporated and coevaporated with toluene. The crude product was purified by HPLC (MeOH/ water 6:4 + 0.5% TFA followed by MeOH/ water 4:1 + 0.2% TFA) to give compound 40 (13 mg, 67 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CD_3OD$) δ 0.82-0.98 (m, 1H), 1.01 (s, 9H), 1.05-1.26 (m, 3H), 1.34-1.43 (m, 1H), 1.49-1.77 (m, 8H), 2.10-2.21 (m, 1H), 2.28-2.42 (m, 2H), 2.50-2.61 (m, 1H), 2.64 (s, 3H), 2.68-2.81 (m, 1H), 3.36-3.45 (m, 2H), 4.04-4.11 (m, 1H), 4.06 (s, overlapped, 3H), 4.27 (d, *J* = 8.8 Hz, 1H), 5.10 (dd, *J* = 1.8, 10.3 Hz, 1H), 5.28 (dd, *J* = 1.8, 17.2 Hz, 1H), 5.59-5.68 (m, 1H), 5.82 (ddd, *J* = 9.1, 10.3, 17.2 Hz, 1H), 7.44 (dd, *J* = 2.5, 11.8 Hz, 1H), 7.50 (s, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.69-7.78 (m, 3H), 8.02-8.07 (m, 2H), 8.39 (d, *J* = 9.3 Hz, 1H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$) δ 23.5, 26.0, 26.9, 27.2, 27.3, 30.0, 30.7, 34.7, 35.3, 37.0, 38.7, 41.0, 41.3, 47.4, 56.9, 59.4, 62.7, 83.9, 100.4, 102.2, 116.2, 117.7, 121.7, 126.7, 129.8, 130.8, 133.4, 133.9, 135.6, 143.5, 158.0, 166.6, 168.6, 172.5, 173.4, 173.6, 175.4, 176.4. Maldi-

TOF-spectrum: $(M+H)^+$ calcd: 782.4, found: 782.2; $(M+Na)^+$ calcd: 804.4, found: 804.2; $(M+K)^+$ calcd: 820.5, found: 820.2.

Example 41

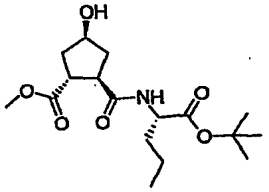


3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid methyl ester (41)

Compound 32 (1.014 g, 6.50 mmol) was dissolved in acetone (35 mL) before methyl iodide (13.68 g, 96.4 mmol) and silver(I)oxide (1.61 g, 6.95 mmol) were added. After stirring for 3h the mixture was filtered through celite and the filtrate was evaporated before purification by flash column chromatography (toluene/ethyl acetate 4:1) was performed yielding the methyl ester 41 (702 mg, 64 %) as white crystals.

$^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ 1.96 (d, $J$ = 10.7 Hz, 1H), 2.21-2.25 (m, 3H), 2.91-2.95 (m, 1H), 3.16 (s, 1H), 3.75 (s, 3H), 4.98 (app. s, 1H).

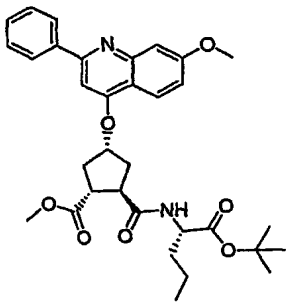
Example 42



(1*R*,2*R*,4*S*)-2-((*S*)-1-*tert*-Butoxycarbonyl-butylcarbamoyl)-4-hydroxy-cyclopentanecarboxylic acid methyl ester (42)

Compound 41 (263 mg, 1.55 mmol) and H-Nva-O*t*Bu (420 mg, 2.42 mmol) were dissolved in dry THF (20 mL). DIEA (530 µL, 3.04 mmol) and 2-hydroxypyridine (260 mg, 2.73 mmol) were added and the mixture was refluxed for five days. The solvent was evaporated and the crude product was purified by flash column chromatography (toluene/ EtOAc 1:2) to give 42 (510 mg, 96%).

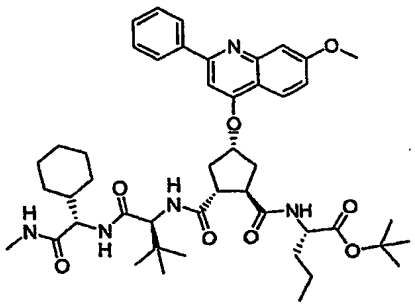
Example 43



(1*R*,2*R*,4*R*)-2-((*S*)-1-*tert*-Butoxycarbonyl-butylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid methyl ester (43)

Compound 42 (249 mg, 0.725 mmol), 2-phenyl-7-methoxy-4-quinolinol (310 mg, 1.23 mmol) and $PPh_3$ (580 mg, 2.21 mmol) were dissolved in dry THF and the temperature was lowered to 0°C. DIAD (435 µL. 2.21 mmol) dissolved in 2 mL dry THF, was added to the mixture during five minutes. After two hours the temperature was raised to room temperature and the solution was stirred overnight. Evaporation and purification by flash column chromatography (toluene/ EtOAc gradient 6:1 to 4:1) gave 43 (324 mg, 78%).

Example 44

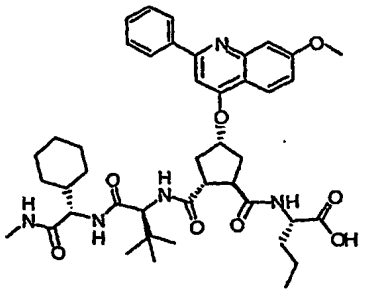


(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid *tert*-butyl ester (44)

Compound 43 (38 mg, 0.066 mmol) was dissolved in dioxane/ water 1:1 (4 mL) and the solution was cooled to 0 °C and 1 M LiOH (132 µl, 0.132 mmol) was added. The temperature was raised to room temperature and the solution was stirred for 2 hours after which it was neutralized by addition of 1M HCl and evaporated and coevaporated with toluene. The residue and deprotected amine 38 (1.1 eq) was dissolved in DMF and coupled using the standard HATU coupling conditions as in the synthesis of compound 34. The crude product was extracted with EtOAc, washed with brine, dried, filtered and concentrated. Purification with HPLC (MeOH/ water 9:1 + 0.2% TEA) provided compound 44 (44 mg, 81 %) as a colorless solid.

$^1$H-NMR ($CDCl_3$, 300 MHz) rotamers (5:1) δ 0.79 (t, $J$ = 7.3 Hz, 3H), 0.85-1.19 (m, 3H), 0.93 (s, overlapped, 9H), 1.20-1.35 (m, 2H), 1.39 (s, 1.5 H), 1.43 (s, 7.5 H), 1.54-1.79 (m, 6H), 2.06-2.28 (m, 3H), 2.39-2.51 (m, 2H), 2.66-2.78 (m, 1H), 2.74 (d, overlapped, $J$ = 4.7 Hz, 3H), 3.42-3.68 (m, 2H), 3.84 (s, 2.5 H), 3.88 (s, 0.5 H), 4.19 (t, $J$ = 8.9 Hz, 1H), 4.39-4.59 (m, 1H), 4.68 (d, $J$ = 9.6 Hz, 1H), 5.04-5.14 (m, 1H), 6.77 (s, 1H), 6.88-7.06 (m, 2H), 7.26-7.47 (m, 6H), 7.53 (b, 1H), 7.85-7.97 (m, 3H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$) δ 13.7, 18.7, 25.6, 25.7, 26.0, 26.7, 28.0, 28.9, 29,7, 34.5, 34.7, 37.7, 38.0, 39.2, 46.6, 47.7, 52.7, 55.3, 58.5, 60.3, 77.9, 81.7, 98.0, 107.4, 115.0, 117.9, 122.8, 127.4, 128.6, 129.0, 140.2, 151.2, 158.9, 160.6, 161.1, 170.9, 171.6, 171.8, 172.7, 173.3. Maldi-TOF-spectrum: $(M+H)^+$ calcd: 828.5, found: 828.6; $(M+Na)^+$ calcd: 850.5, found: 850.6; $(M+K)^+$ calcd: 866.6, found: 866.6.

Example 45



(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (45)

Compound 44 (21 mg, 0.025 mmol) was dissolved in $CH_2Cl_2$ (1.5 mL) and triethylsilane (10 µL, 0.063 mmol) and TFA (1.5 mL) were added. The solution was stirred for 2 hours at room temperature after which the solvents were evaporated and coevaporated with toluene to provide compound 45 (20 mg, 100 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CD_3OD$) δ 0.93 (t, overlapped, 3H), 0.98 (s, 9H), 0.99-1.25 (m, 4H), 1.30-1.49 (m, 3H), 1.50-1.90 (m, 8H), 2.25-2.39 (m, 2H), 2.54-2.62 (m, 1H), 2.64 (s, 3H), 2.72-2.87 (m, 1H), 3.34-3.57 (m, 3H), 4.02-4.13 (m, 1H), 4.06 (s, overlapped, 3H), 4.27-4.36 (m, 1H), 4.37-4.47 (m, 1H), 5.57-5.66 (m, 1H), 7.45 (dd, *J* = 2.3, 9.2 Hz, 1H), 7.48 (s, 1H), 7.54 (d, *J* = 2.2 Hz, 1H), 7.69-7.79 (m, 3H), 8.01-8.07 (m, 2H), 8.42 (d, *J* = 9.3 Hz, 1H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$) δ 14.0, 20.2, 26.0, 26.9, 27.2, 30.1, 30.7, 34.6, 35.3, 37.2, 39.1, 41.2, 47.7, 53.7, 56.9, 59.4, 59.5, 62.5, 83.7, 100.4, 101.3, 102.2, 116.2, 121.7, 126.7, 129.8, 130.8, 133.3, 133.9, 143.5, 157.9, 166.6, 168.5, 172.5, 173.6, 175.3, 175.4, 175.5.

Maldi-TOF-spectrum: $(M+H)^+$ calcd: 772.4, found: 772.6; $(M+Na)^+$ calcd: 794.4, found: 794.6; $(M+K)^+$ calcd: 810.5, found: 810.6.

Example 46

Hept-6-enal (46)

To a solution of hept-6-en-1-ol (1 mL, 7.44 mmol) and N-methylmorpholine N-oxide (1.308 g, 11.17 mmol) in DCM (17 mL) was added ground molecular sieves (3.5 g, 4 Å). The mixture was stirred for 10 min at room temperature under nitrogen atmosphere before tetrapropylammonium perruthenate (TPAP) (131 mg, 0.37 mmol) was added. After stirring for additional 2.5 h the solution was filtered through celite.

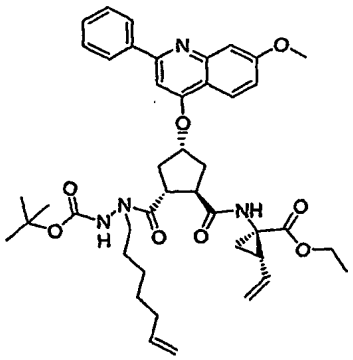
The solvent was then carefully evaporated and the remaining liquid was purified by flash column chromatography (DCM) to give the volatile aldehyde 46 (620 mg, 74%) as an oil.

Example 47

*N*'-Hept-6-en-(*E*)-ylidene-hydrazinecarboxylic acid *tert*-butyl ester (47)

To a solution of 46 (68 mg, 0.610 mmol) and *tert*-butyl carbazate (81 mg, 0.613 mmol) in MeOH (5 mL) was added ground molecular sieves (115 mg, 3Å). The mixture was stirred for 3 h after which it was filtered through celite and evaporated. The residue was dissolved in dry THF (3 mL) and AcOH (3mL). $NaBH_3CN$ (95 mg, 1.51 mmol) was added and the solution was stirred over night. The reaction mixture was diluted with saturated $NaHCO_3$ solution (6 mL) and EtOAc (6 mL). The organic phase was washed with brine, saturated $NaHCO_3$, brine, dried over $MgSO_4$ and evaporated. The cyanoborane adduct was hydrolyzed by treatment with MeOH (3 mL) and 2 M NaOH (1.9 mL). The mixture was stirred for 2 h and the MeOH was evaporated. $H_2O$ (5 mL) and DCM (5 mL) were added and the water phase was extracted three times with DCM. The combined organic phases were dried and evaporated. Purification by flash column chromatography (toluene/ethyl acetate 9:1 with 1 % triethylamine and toluene/ethyl acetate 6:1 with 1 % triethylamine) provided 47 (85 mg, 61 %) as an oil.

Example 48

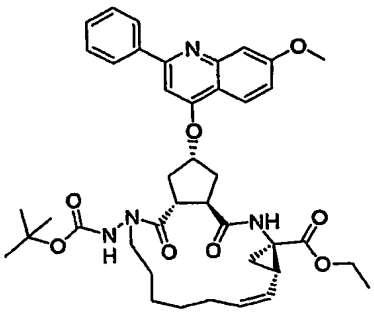


(1*R*,2*S*)-1-{[(1*R*,2*R*,4*R*)-2-(*N'-tert*-Butoxycarbonyl-*N*-hept-6-enyl-hydrazinocarbonyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (48)

Scaffold molecule 35 (135 mg, 0.225 mmol) and triethylsilane (71 µL, 0.447 mmol) was dissolved in DCM (2 mL) after which trifluoroacetic acid (TFA) (2 mL) was added. The mixture was stirred for 2 h and thereafter co-evaporated with toluene in order to remove the TFA. The residue was dissolved in DMF (3 mL) and 47 (60 mg, 0.263 mmol) and DIEA (118 µL, 0.677 mmol) were added. The temperature was lowered to 0° C and the coupling reagent *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (94 mg, 0.247 mmol) was added. The cold solution was allowed to stir for half an hour and then for additional 16 h in room temperature. The solvent was removed by heating the reaction flask in a water bath under diminished pressure. The residue was thereafter dissolved in ethyl acetate and the organic phase was washed three times with brine, dried, filtered and evaporated. Purification by HPLC (MeOH/$H_2O$ 90:10 with 0.2 % triethylamine) gave 48 (140 mg, 82 %) as an oil.

$^1$H-NMR (300 MHz, $CDCl_3$, 40° C): δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.28-1.42 (m, 6H), 1.46 (s, 9H), 1.52-1.62 (m, 2H), 1.82-1.91 (m, 1H), 1.96-2.16 (m, 3H), 2.18-2.34 (m, 2H), 2.42-2.56 (m, 1H), 2.58-2.72 (m, 1H), 3.42 (app. bs, 3H), 3.66-3.84 (m, 1H), 3.92 (s, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.88-5.02 (m, 2H), 5.07-5.18 (m, 2H), 5.20-5.32 (m, 1H), 5.63-5.84 (m, 2H), 6.62 (bs, 1H), 6.94 (s, 1H), 7.09 (dd, *J* = 2.6, 9.2 Hz, 1H), 7.36-7.51 (m, 4H), 7.99-8.10 (m, 3H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$): δ 14.3, 23.0, 26.4, 26.6, 28.3, 28.6, 33.2, 33.5, 35.6, 37.6, 40.6, 44.7, 47.1, 48.6, 55.5, 61.5, 81.9, 98.4, 107.9, 114.5, 115.6, 118.1, 123.2, 127.6, 128.3, 128.7, 129.1, 133.5, 138.7, 140.7, 151.5, 154.5, 159.2, 160.9, 161.5, 170.5, 174.2, 176.3.

Example 49

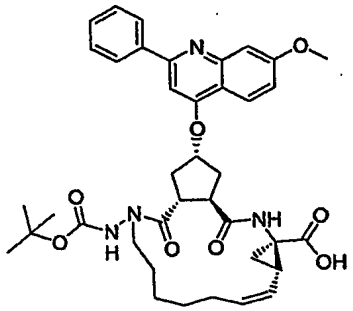


(*Z*)-(1*R*,4*R*,6*S*,16*R*,18*R*)-14-*tert*-Butoxycarbonylamino-18-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,15-dioxo-3,14-diaza-tricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carboxylic acid ethyl ester (49)

A solution of 48 (158 mg, 0.209 mmol) in dry DCM (25 mL) was bubbled with argon for 5 min. To the stirred solution under argon atmosphere was then added a solution of Hoveyda-Grubbs catalyst 2$^{nd}$ generation (11 mg, 0.018 mmol) in dry DCM (5 mL). The mixture was stirred at reflux under argon atmosphere for 16 h. The solvent was evaporated and purification by HPLC (MeOH/$H_2O$ 90:10 with 0.2 % triethylamine) yielded 49 (107 mg, 70 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CD_3OD$): δ 1.03-1.22 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.32-1.44 (m, 4H), 1.49 (s, 9H), 1.55-1.73 (m, 2H), 1.81-1.91 (m, 1H), 2.04-2.28 (m, 3H), 2.30-2.52 (m, 3H), 2.53-2.70 (m, 1H), 2.86-3.00 (m, 1H), 3.34-3.44 (m, 1H), 3.46-3.62 (m, 1H), 3.95 (s, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.32-4.48 (m, 1H), 5.20-5.33 (m, 1H), 5.34 (bs, 1H), 5.58-5.70 (m, 1H), 7.10 (s, 1H), 7.14 (dd, *J* = 2.5, 9.1 Hz, 1H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.45-7.55 (m, 3H), 8.00 (d, *J* = 8.0 Hz, 2H), 8.17 (d, *J* = 9.3 Hz, 1H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$): *δ* 14.6, 23.4, 27.5, 27.7, 28.0, 28.5, 30.7, 36.1, 38.1, 42.5, 45.6, 56.0, 62.7, 79.9, 82.8, 100.2, 107.4, 116.6, 119.1, 124.5, 126.5, 128.9, 129.8, 130.5, 135.8, 141.5, 152.2, 156.4, 161.3, 162.5, 163.1, 171.9, 175.8, 179.0. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 727.4, found: 727.5.

Example 50

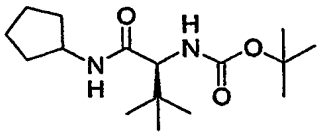


(*Z*)-(1*R*,4*R*,6*S*,16*R*,18*R*)-14-*tert*-Butoxycarbonylamino-18-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,15-dioxo-3,14-diaza-tricyclo[14.3.0.0$^{4,6}$]nonadec-7-ene-4-carboxylic acid (50)

To a solution of 49 (27 mg, 0.037 mmol) in THF/MeOH/$H_2O$ 2:1:1 (5 mL) was added 1 M LiOH (300 µL, 0.300 mmol). The solution was stirred for 24 h at room temperature and finally for one hour at reflux. After acidification to pH 3-4 with 1 M HCl and evaporation the residue was purified by HPLC (MeOH/$H_2O$ 80:20 and MeOH/$H_2O$ 90:10) providing 50 (12 mg, 46 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CD_3OD$): δ 1.06-1.24 (m, 1H), 1.26-1.42 (m, 3H), 1.48 (s, 9H), 1.52-1.73 (m, 3H), 1.80-1.90 (m, 1H), 2.02-2.15 (m, 1H), 2.15-2.40 (m, 4H), 2.43-2.54 (m, 1H), 2.54-2.68 (m, 1H), 2.88-3.00 (m, 1H), 3.35-3.48 (m, 1H), 3.49-3.66 (m, 1H), 3.96 (s, 3H), 4.32-4.48 (m, 1H), 5.25-5.42 (m, 2H), 5.56-5.68 (m, 1H), 7.14 (s, 1H), 7.17 (dd, *J* = 2.5, 9.1 Hz, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.46-7.58 (m, 3H), 8.00 (d, *J* = 8.0 Hz, 2H), 8.19 (d, *J* = 9.1 Hz, 1H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$): *δ* 23.6, 26.8, 27.8, 28.3, 28.5, 30.5, 35.8, 38.1, 43.0, 45.5, 56.0, 80.2, 82.7, 100.4, 106.9, 116.6, 119.2, 124.7, 127.4, 129.0, 129.8, 130.7, 134.8, 140.9, 151.6, 156.5, 161.1, 163.0, 163.4, 173.8, 175.7, 179.3.

Example 51

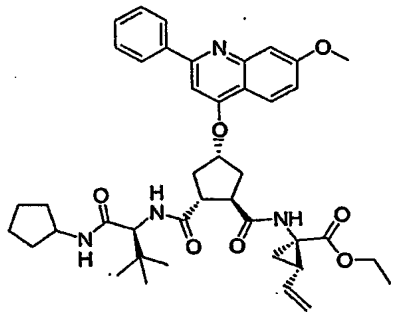


((*S*)-1-Cyclopentylcarbamoyl-2,2-dimethyl-propyl)-carbamic acid *tert*-butyl ester (51)

To a cold solution of 36 (133 mg, 0.575 mmol), cyclopentylamine (64 µL, 0.648 mmol) and DIEA (301 µL, 1.73 mmol) in DMF (3 mL) was added the coupling reagent HATU (240 mg, 0.631 mmol). The mixture was stirred for half an hour and for additional two hours at room temperature. The solvent was removed by heating the reaction flask in a water bath under diminished pressure and the residue was dissolved in ethyl acetate, after which the organic phase was washed three times with brine, dried, filtered and evaporated. Purification by flash column chromatography (toluene/ethyl acetate 4:1) provided 51 (140 mg, 82 %) as colorless crystals.

$^1$H-NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 9H), 1.28-1.48 (m, overlapped, 2H), 1.40 (s, 9H), 1.49-1.71 (m, 4H), 1.86-2.01 (m, 2H), 3.76 (b, 1H), 4.09-4.23 (m, 1H), 5.32 (b, 1H), 5.91 (b, 1H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$): *δ* 23.6, 23.7, 26.5, 28.3, 32.6, 33.1, 34.5, 51.0, 62.2, 79.4, 155.9, 170.3.

Example 52

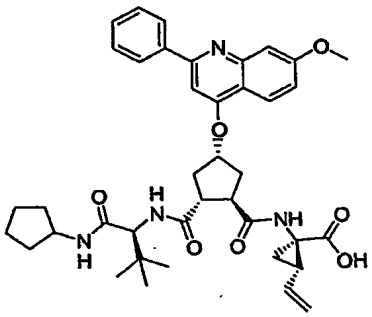


(1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-((*S*)-1-Cyclopentylcarbamoyl-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (52)

Compound 51 (298 mg, 0.048 mmol) and 35 (16 mg, 0.054 mmol) was deprotected and coupled according to the method for the preparation of 39. Purification by HPLC (MeOH/$H_2O$ 90:10 with 0.2 % triethylamine) gave 52 (22 mg, 63 %) as a colorless solid.

$^1$H-NMR ($CDCl_3$, 300 MHz): δ 0.97 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.26-1.37 (m, 1H), 1.38-1.46 (m, 2H), 1.48-1.58 (m, 4H), 1.78-1.85 (m, 1H), 1.86-2.02 (m, 3H), 2.03-2.19 (m, 1H), 2.28-2.40 (m, 2H), 2.41-2.54 (m, 1H), 2.64-2.78 (m, 1H), 3.10-3.24 (m, 1H), 3.30-3.44 (m, 1H), 3.95 (s, 3H), 4.04-4.21 (m, 3H), 5.12 (dd, *J* = 1.7, 10.3 Hz, 1H), 5.14-5.22 (m, 1H), 5.28 (dd, *J* = 1.7, 17.0 Hz, 1H), 5.59 (b, 1H), 5.75 (ddd, *J* = 8.8, 10.3, 17.0 Hz, 1H), 6.66-6.82 (m, 2H), 6.99 (s, 1H), 7.09 (dd, *J* = 2.5, 9.1 Hz, 1H), 7.41-7.55 (m, 4H), 7.99-8.09 (m, 3H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$): *δ* 14.3, 22.9, 23.6, 23.6, 26.7, 32.7, 33.2, 33.7, 34.8, 35.9, 36.6, 40.2, 46.4, 47.5, 51.3, 55.5, 61.1, 61.4, 78.0, 98.4, 107.1, 115.2, 117.9, 118.2, 123.1, 127.6, 128.8, 129.3, 133.5, 159.1, 161.4, 169.4, 169.9, 173.1, 174.0. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 725.4, found: 725.6; $(M+Na)^+$ calcd: 747.4, found: 747.6; $(M+K)^+$ calcd: 763.3, found: 763.5.

Example 53

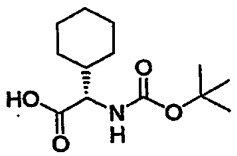


(1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-((*S*)-1-Cyclopentylcarbamoyl-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (53)

To a solution of 52 (14 mg, 0.019 mmol) in dioxane/$H_2O$ 1:1: (4 mL) was added 1 M LiOH (115 µL, 0.115 mmol). The solution was stirred for 24 h at room temperature. Thereafter an additional portion of LiOH (75 µL, 0.075 mmol) was added and the solution was stirred for another 24 h. After acidification to approximately pH 3 with 1 M HCl and co-evaporation with toluene the residue was purified by HPLC (MeOH/$H_2O$ 70:30 with 0.2 % TFA) yielding 53 (8 mg, 60 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CD_3OD$): δ 0.98 (s, 9H), 1.28-1.48 (m, 3H), 1.49-1.76 (m, 5H), 1.78-1.94 (m, 2H), 2.10-2.24 (m, 1H), 2.26-2.45 (m, 2H), 2.50-2.62 (m, 1H), 2.66-2.79 (m, 1H), 3.35-3.48 (m, 2H), 3.94-4.03 (m, 1H), 4.06 (s, 3H), 4.16-4.24 (m, 1H), 5.10 (dd, *J* = 1.8, 10.3 Hz, 1H), 5.29 (dd, *J* = 1.8, 17.2 Hz, 1H), 5.62 (b, 1H), 5.82 (ddd, *J* = 9.1, 10.3, 17.2 Hz, 1H), 7.43 (dd, *J* = 2.5, 9.3 Hz, 1H), 7.50 (s, 1H), 7.50-7.69 (dd, overlapped, 1H), 7.67-7.80 (m, 3H), 8.01-8.11 (m, 2H), 8.39 (d, *J* = 9.3 Hz, 1H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$): *δ* 24.7, 24.7, 27.3, 33.1, 33.6, 34.7, 35.4, 36.9, 38.7, 41.0, 47.4, 52.3, 56.9, 62.3, 83.9, 100.4, 102.3, 116.2, 117.7, 121.6, 126.7, 129.8, 130.8, 133.4, 133.8, 135.6, 143.5, 158.0, 166.5, 168.6, 171.9, 173.4, 175.2, 176.4. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 697.4, found: 697.3; $(M+Na)^+$ calcd: 718.7, found: 719.3; $(M+K)^+$ calcd: 735.3, found: 735.3.

Example 54

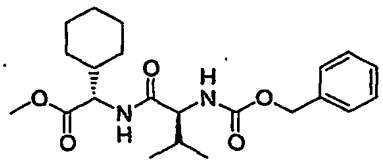



(*S*)-*tert*-Butoxycarbonylamino-cyclohexyl-acetic acid methyl ester (54)

To a solution of Boc-Chg-OH (53 mg, 0.206 mmol) in acetone (3 mL) were added methyl iodide (195 µL, 3.1 mmol) and silver (I) oxide (53 mg, 0.229 mmol). The mixture was allowed to stir over night in a reaction flask that was covered with aluminium foil. Thereafter the solution was filtered through celite and evaporated. Purification by flash column chromatography (toluene/ethyl acetate 15:1) provided methyl ester 54 (56 mg, 100 %) as a colorless oil.

$^1$H-NMR (300 MHz, $CDCl_3$): δ 1.00-1.34 (m, 5H), 1.44 (s, 9H), 1.54-1.82 (m, 6H), 3.73 (s, 3H), 4.20 (dd, *J* = 2.8, 5.0 Hz, 1H), 5.05 (bs, 1H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$): *δ* 26.0, 28.2, 28.3, 29.5, 41.1, 52.0, 58.3, 79.7, 155.6, 172.9.

Example 55

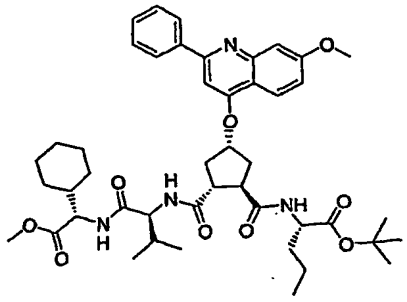


(*S*)-((*S*)-2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (55)

Compound 54 (93 mg, 0.343 mmol) was deprotected and coupled to Z-Val-OH (95 mg, 0.378 mmol) according to the method for the preparation of 39. Flash column chromatography (toluene/ethyl acetate 4:1) gave 55 (131 mg, 94 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CDCl_3$): δ 0.92-1.30 (m, 11H), 1.54-1.88 (m, 6H), 2.02-2.18 (m, 1H), 3.72 (s, 3H), 4.05-4.18 (m, 1H), 4.52 (dd, *J* = 3.0, 5.5 Hz, 1H), 5.12 (s, 2H), 5.49 (bs, 1H), 6.52 (bs, 1H), 7.34 (s, 5H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$): *δ* 17.8, 19.0, 25.8, 28.2, 29.3, 31.2, 40.5, 51.9, 56.8, 60.0, 66.8, 127.7, 127.9, 128.1, 128.3, 136.2, 156.3, 171.3, 172.2.

Example 56

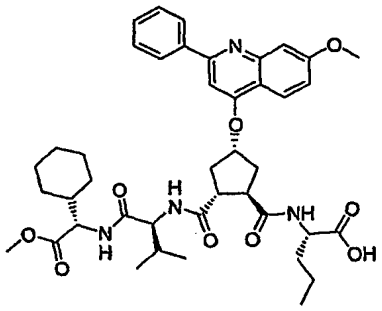


(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid *tert*-butyl ester (56)

To a solution of 55 (40 mg, 0.099 mmol) in ethanol (95%) (7.5 mL) was added palladium on active carbon (10 %, 40 mg) and the mixture was hydrogenated under pressure at room temperature for 2 h. The mixture was filtered through celite and evaporated. Compound 43 (38 mg, 0.083 mmol) was dissolved in dioxane/$H_2O$ 1:1 (3 mL) and the mixture was cooled to 0° C before 1 M LiOH (140 µL, 0.140 mmol) was added to the stirred solution. After 1h the mixture was neutralized with 1 M hydrochloric acid and the solvent was evaporated and co-evaporated with toluene. The residue was coupled to deprotected 55 using the same HATU coupling conditions as in the synthesis of compound 48. Purification by HPLC (MeOH/$H_2O$ 90:10 with 0.2 % triethylamine) gave 56 (56 mg, 88 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CDCl_3$): δ 0.82-0.96 (m, 9H), 0.82-1.22 (m, overlapped, 6H), 1.23-1.40 (m, 2H), 1.44 (s, 9H), 1.50-1.69 (m, 4H), 1.71-1.87 (m, 2H), 1.95-2.06 (m, 1H), 2.07-2.22 (m, 1H), 2.28-2.54 (m, 3H), 2.60-2.75 (m, 1H), 3.08-3.28 (m, 1H), 3.30-3.49 (m, 1H), 3.70 (s, 3H), 3.94 (s, 3H), 4.28-4.38 (m, 1H), 4.41-4.57 (m, 2H), 5.17 (b, 1H), 6.54-6.70 (m, 2H), 6.74 (b, 1H), 6.95 (s, 1H), 7.09 (dd, $J$ = 2.5, 9.1 Hz, 1H), 7.39-7.55 (m, 5H), 7.98-8.10 (m, 3H); $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta$ 13.7, 18.1, 18.6, 19.2, 25.9, 28.0, 28.2, 29.6, 30.7, 34.6, 36.5, 37.6, 40.8, 47.4, 47.5, 52.1, 52.8, 55.5, 56.8, 58.9, 77.8, 82.0, 98.3, 107.5, 115.3, 118.1, 123.1, 127.5, 128.7, 129.1, 140.5, 151.4, 159.2, 160.7, 161.3, 171.0, 171.5, 172.3, 172.8, 173.0. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 815.5, found: 815.7; $(M+Na)^+$ calcd: 837.4, found: 837.6; $(M+K)^+$ calcd: 853.4, found: 853.6.

Example 57

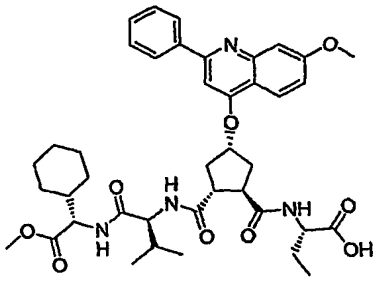


(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (57)

*Tert.*butyl ester 56 (28 mg, 0.034 mmol) and triethylsilane (14 µL, 0.088 mmol) was dissolved in DCM (2 mL) after which trifluoroacetic acid (2 mL) was added and the mixture was stirred for 2 h. Co-evaporation with toluene gave 57 (26 mg, 100 %) as a colorless solid.

$^1$H-NMR (300 MHz, $CD_3OD$): δ 0.86-1.00 (m, 9H), 1.01-1.24 (m, 4H), 1.36-1.46 (m, 2H), 1.48-1.75 (m, 8H), 1.70-1.89 (m, overlapped, 1H), 1.96-2.12 (m, 1H), 2.22-2.40 (m, overlapped, 2H), 2.49-2.64 (m, 1H), 2.72-2.91 (m, 1H), 3.26-3.40 (m, overlapped, 1H), 3.50-3.68 (m, overlapped, 1H), 3.62 (s, 3H), 4.05 (s, 3H), 4.09-4.17 (m, 1H), 4.17-4.25 (m, 1H), 4.35-4.45 (m, 1H), 5.62 (b, 1H), 7.44 (dd, $J$ = 2.2, 9.3 Hz, 1H), 7.49 (s, 1H), 7.53 (d, $J$ = 2.2 Hz, 1H), 7.65-7.78 (m, 3H), 7.98-8.06 (m, 2H), 8.41 (dd, $J$ = 2.8, 9.3 Hz, 1H); $^{13}$C-NMR ($CD_3OD$, 75.5 MHz): δ 13.9, 18.8, 19.7, 20.2, 27.0, 29.7, 30.5, 31.8, 34.6, 37.7, 38.9, 41.1, 47.8, 52.3, 53.6, 56.9, 58.8, 58.9, 60.3, 83.8, 100.4, 102.2, 116.2, 121.6, 126.7, 129.8, 130.8, 133.3, 133.8, 143.5, 157.9, 166.5, 168.5, 173.3, 173.9, 175.5, 175.5, 175.6. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 759.4, found: 759.7; $(M+Na)^+$ calcd: 781.4, found: 781.7; $(M+K)^+$ calcd: 797.4, found: 797.7.

Example 58

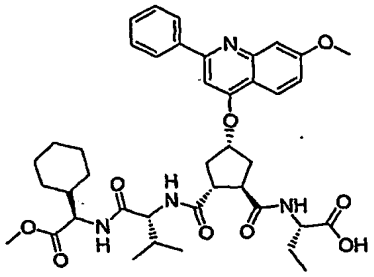


(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-butyric acid (58)

The procedure described in example 42 was followed but with the use of L-2-amino-N-butyric acid tert.butyl ester instead of H-Nva-O*t*Bu. The afforded compound was then reacted as described in example 43 which gave (1*R*,2*R*,4*R*)-2-((*S*)-1-*tert*-butoxycarbonyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid methyl ester. Coupling of this compound with 55 as described in example 56 followed by esterhydrolysis as described in example 57 gave 58 as a colourless solid.

$^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ 0.82-0.99 (m, 9H), 0.82-1.40 (m, overlapped, 6H), 1.48-1.78 (m, 6H), 1.80-1.95 (m, 1H), 1.97-2.12 (m, 1H), 2.22-2.40 (m, overlapped, 2H), 2.51-2.64 (m, 1H), 2.71-2.90 (m, 1H), 3.16-3.39 (m, overlapped, 1H), 3.49-3.59 (m, 1H), 3.63 (s, 3H), 3.95 (s, 3H), 4.12-4.23 (m, 2H), 4.28-4.38 (m, 1H), 5.31 (b, 1H), 7.43 (dd, $J$ = 2.2, 9.3 Hz, 1H), 7.47 (s, 1H), 7.51 (s, 1H), 7.66-7.89 (m, 3H), 7.99-8.07 (m, 2H), 8.42 (d, $J$ = 9.1 Hz, 1H); $^{13}$C-NMR (75.5 MHz, $CD_3OD$): $\delta$ 10.7, 18.8, 19.7, 25.8, 27.0, 27.0, 29.7, 30.5, 31.8, 37.7, 38.9, 41.2, 47.9, 52.3, 55.3, 56.9, 58.8, 60.6, 83.6, 100.7, 102.2, 116.3, 121.5, 126.7, 129.8, 130.8, 133.7, 133.8, 143.9, 158.2, 166.4, 168.3, 173.3, 173.8, 175.2, 175.5, 175.6. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 745.4, found: 744.9; $(M+Na)^+$ calcd: 767.4, found: 766.9; $(M+K)^+$ calcd: 783.5, found: 782.9.

Example 59

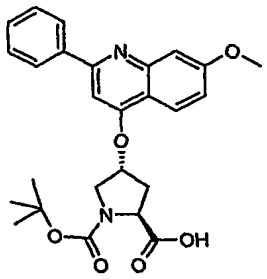


(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*R*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-butyric acid (59)

The procedure described in example 54 was followed but with the use of Boc-D-cyclohexylglycine instead of Boc-L-cyclohexylglycine. The afforded compound was then reacted as described in example 55 followed by coupling with (1*R*,2*R*,4*R*)-2-((*S*)-1-*tert*-Butoxycarbonyl-pentylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid methyl ester as described in example 56. Removal of the ester group as described in example 57 gave compound 59 as a colourless solid.

$^1$H-NMR ($CD_3OD$, 300 MHz): $\delta$ 0.82-1.02 (m, 9H), 1.04-1.42 (m, 6H), 1.52-1.80 (m, 6H), 1.80-1.96 (m, overlapped, 1H), 2.00-2.14 (m, 1H), 2.29-2.46 (m, 2H), 2.51-2.65 (m, 1H), 2.68-2.84 (m, 1H), 3.24-3.39 (m, overlapped, 1H), 3.47-3.60 (m, 1H), 3.67 (s, 3H), 4.07 (s, 3H), 4.18-4.27 (m, 2H), 4.28-4.38 (m, 1H), 5.64 (app. bs, 1H), 7.44 (d, $J$ = 2.3, 6.9 Hz, 1H), 7.42 (s, 2H), 7.67-7.81 (m, 3H), 8.04 (d, $J$ = 7.8 Hz, 2H), 8.41 (d, $J$ = 9.1 Hz, 1H); $^{13}$C-NMR ($CD_3OD$, 75.5 MHz): $\delta$ 10.8, 18.5, 19.6, 25.7, 27.1, 27.1, 30.1, 30.6, 31.9, 37.3, 38.2, 41.1, 47.8, 52.3, 55.4, 56.9, 59.0, 59.1, 60.2, 83.8, 100.5, 102.2, 116.3, 121.6, 126.8, 129.8, 130.8, 133.6, 133.8, 143.7, 158.1, 166.5, 168.5, 173.4, 173.8, 175.4, 175.7, 175.7. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 745.4, found: 745.4; $(M+Na)^+$ calcd: 767.4, found: 767.4; $(M+K)^+$ calcd: 783.5, found: 783.3.

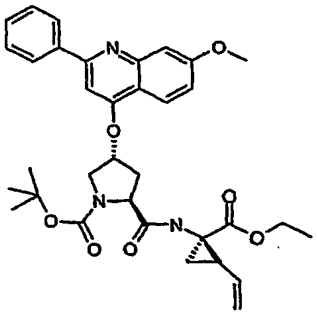
Example 60



N-Boc-4R-(2-phenyl-7-methoxyquinoline-4-oxo)proline (60)

To a stirred solution of N-Boc–trans-4-hydroxy-L-proline (3.9 g, 16.9 mmol) in DMSO (90mL) was added potassium tert.butoxide (4.5 g, 40.1 mmol). After 1 hrs 4-chloro-2-phenyl-7-methoxy quinoline (4.5g, 16.7 mmol) was added and stirred at RT for 12 hrs. The mixture was diluted with water (180 mL), washed with ethyl acetate (1x30mL) and neutralized with 1N HCl. The solid was filtered, washed with water and dried giving (4.65g, 10mmol) of product. >95% purity by HPLC. $M+H^+$ 464.2.

Example 61

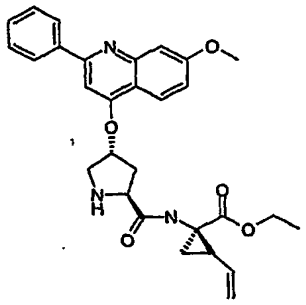


2-(1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(7-methoxy-2-phenyl-quinoline-4-yloxy)-pyrrolidine-1-carboxylic acid *tert*.butyl ester (61)

To a solution of 1-amino-2-vinyl-cyclopropanecarboxylic acid ethyl ester (41 mg, 0.26 mmol), 60 (11 mg, 0.22 mmol), HATU (204 mg, 0.54 mmol) in DMF (4 mL) was added diisopropyehtylamine (187 µL, 1.08 mmol). After stirring at RT for 1 hrs, dichloromethane (4 mL) was added. The solution was washed with aqueous

$NaHCO_3$ (sat) and with two portions of water. The organic layer was dried and concentrated. The product was pure enough (>95 % by HPLC) to be used in the next step. $M+H^+$ 602.2.

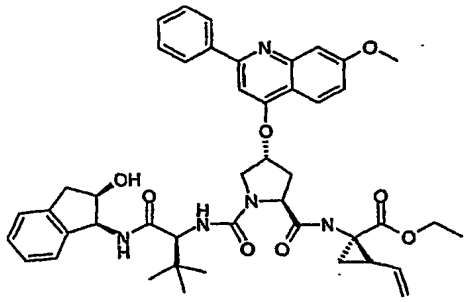
Example 62



1-{[4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (62)

Compound 61 was kept in TFA-DCM 1:2 (3 mL) at RT for 60 min. Toluene (3 mL) was added. The sample was co-evaporated to dryness. Purity by HPLC >95%. $M+H^+$ 502.4.

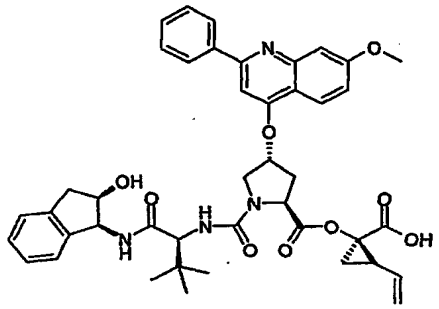
Example 63



1-{[1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (63)

To a solution of compound 62 (0.13 mmol) in THF (2 mL), was added a large excess of $NaHCO_3$ (s) and a solution of phosgene in toluene (1.6 M, 600 µL). After 10 min of agitation the slurry was filtered and concentrated to dryness. The solid was redissolved in dichloromethane and a large excess of $NaHCO_3$ (s) and 2-Amino-*N*-(2-hydroxy-indan-1-yl)-3,3-dimethyl-butyramide (0.65 mmol) was added. The slurry was agitated for 24-40 hrs at RT. The slurry was filtered, concentrated and subjected to silica column chromatography (gradient elution from 100 % DCM to MeOH/DCM 2:98) to give the title compound (89.6 mg, 0.11 mmol). Purity by HPLC >95%. $M+H^+$ 790.3.

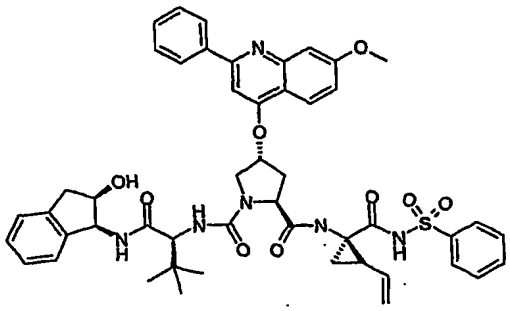
Example 64



1-[1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propyl]-4-(6-methoxy-3-phenyl-naphthalen-1-yloxy)-pyrrolidin-2-yl]-2-vinyl-cyclopropanecarboxylic acid (64)

To a solution of 63 (76.7 mg, 0.097 mmol) in THF-MeOH 2:3 (2 mL) was added 1M LiOH 5 equiv. The solution was kept at 60 °C for 60 min. After cooling to RT, HOAc 15-30 eq. was added followed by toluene (2 mL) and then concentrated to dryness. The residue was taken up in DCM and washed with water. The organic layer was dried and concentrated to give the title compound (72 mg, 0.094 mmol). Purity >95% by HPLC $M+H^+$ 762.2.

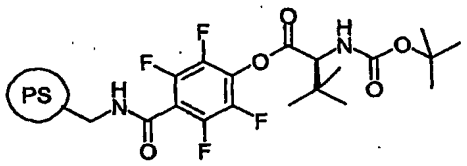
Example 65



*N*-(2-Hydroxy-indan-1-yl)-2-[4-(6-methoxy-3-phenyl-naphthalen-1-yloxy)-2-(1-phenylmethanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-pyrrolidin-1-yl]-3,3-dimethyl-butyramide (65)

To solution of 64 (25 mg, 0.033 mmol) in chloroform (1 mL) was added benzenesulfonamide (10.5 mg, 0.066 mmol) followed by diisopropylethylamine (34 μL, 0.197mmol). The solution was stirred at RT for 10 min and then at -20 °C for 30 min. PyBOP (76 mg, 0.13 mmol) was then added as a solid. The solution was kept at -20 °C for 48 hours. The solution was then poured into aqueous $NaHCO_3$ (sat.) and washed with water. The organic layer was dried, concentrated and subjected to purification by HPLC, affording the title compound as a white solid.

Example 66

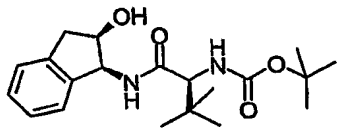


Resin bound 2-tert.butoxycarbonylamino-3,3-dimetylbutyric acid (66)

To Argonaut resin PS-TFP (1.38 mmol/g, 10 g) and 2-*tert*-butoxycarbonylamino-3,3-dimethyl-butyric acid (4.5 g, 20.7mmol) was added dichloromethane (40 mL) and DMF (10 mL). To this mixture was added DMAP (1 g, 8.28 mmol) and then DIC (9.5 mL, 60.7 mmol). After 3 hrs of agitation at RT the resin was filtered and washed

successively with DMF, THF, DCM, THF, DCM and ether and then dried in a vacuum.

Example 67

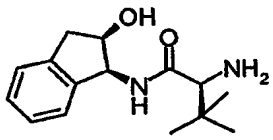


[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propyl]-carbamic acid *tert.*butyl ester (67)

To a portion of 66 (200 mg) in DCM aminoindanol (0.14 mmol) was added. The mixture was agitated for 2 hrs. The liquid was filtered of and the resin washed with 2xDCM. The combined liquids were combined and concentrated to dryness to afford the title compound (20.5 mg, 0.055 mmol) Purity >95% by HPLC. $M+H^+$ 363.15.

$^{13}C$ NMR $\delta_C$ (100 MHz; $CDCl_3$; $Me_4Si$) 27.0, 28.5, 34.2, 39. 8, 50.8, 57.9, 68.2, 73.7, 124.8, 125.6, 127.4, 128.5, 140.4, 171.6. $^1H$ NMR $\delta_H$ (400 MHz; $CDCl_3$; $Me_4Si$) 1.07 (9H, s, $CCH_3$), 1.44 (9H, s, $OCCH_3$), 2.93 (1H, dd, $J_{gem}$16.4 Hz, $J_{3,2}$ 2.3 Hz, $CH_2$), 3.15 (1H, dd, $J_{gem}$16.4 Hz, $J_{3,2}$ 5.2 Hz, $CH_2$),

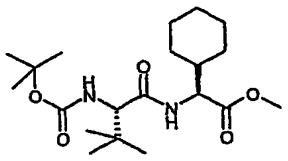
Example 68



2-Amino-*N*-(2-hydroxy-indan-1-yl)-3,3-dimethyl butyramide (68)

Compound 67 was kept in DCM-TFA 2:1 (2 mL) for 60 min at RT. The solution was co-evaporated with toluene to dryness.

Example 69

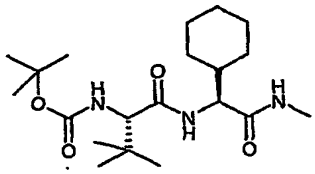


(2-*tert*-Butoxycarbonylamino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (69)

To a solution of 2-*tert*.butoxycarbonylamino-3,3-dimethyl butyric acid (500 mg, 2.16 mmol), Amino-cyclohexyl-acetic acid methyl ester (444 mg, 2.59 mmol) and HATU (2 g, 5.40 mmol) in DMF (20 mL) was added diisopropylethylamine (1.88 mL, 10.8 mmol). The solution was stirred for 1 hrs at r.t. and diluted with dichloromethane (40 mL). This solution was washed with aqueous. NaHCO3 (sat.) and water (x2), dried and concentrated. The product was >95 % pure. $M+H^+$ 385.4.

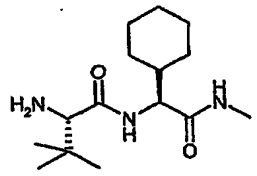
Example 70

{1-[(Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester (70)



To compound 69 in EtOH-THF 1:2 was added a large excess of methylamine (30% in water) and left at rt. for 2 weeks. The solution was concentrated to dryness and the residue subjected to a short silica gel column eluted with 2% MeOH in dichloromethane to give a pure (>95%) product $M+H^+$ 384.5.

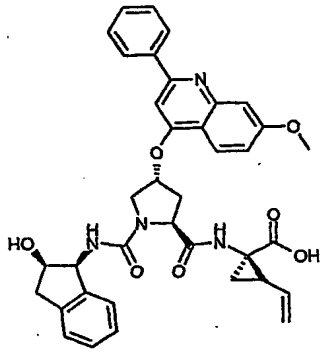
Example 71



2-Amino-*N*-(cyclohexyl-methylcarbamoyl-methyl)-3,3-dimethyl-butyramide (71)

Compound 70 was kept in dichloromethane-trifuoroacetic acid 2:1 for 1 h at rt and concentrated to dryness. The residue was dried in a vacuum for 16 hrs. Reversed phase C18 HPLC showed >95% purity $M+H^+$ 283.1.

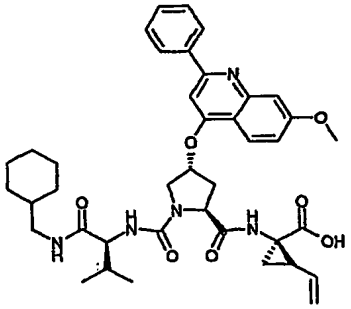
Example 72



(1R,2S)-1-{[(2S,4R)-1-((1S,2R)-2-Hydroxy-indan-1-ylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (72)

Compound 62 was treated as described for the preparation of 63 but with the use of (1S,2R)-cis-1-amino-2-indanol instead of 2-amino-N-(2-hydroxyindan-1-yl)-3,3-dimethyl butyramide followed by ester hydrolysis as described for the preparation of compound 64 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 649.1.

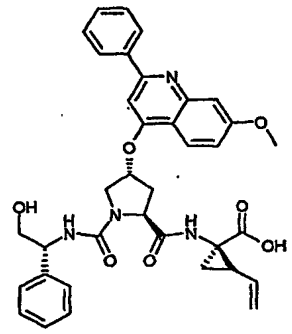
Example 73



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(Cyclohexylmethyl-carbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (73)

N-(tert-butoxycarbonyl)-L-valine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 712.3.

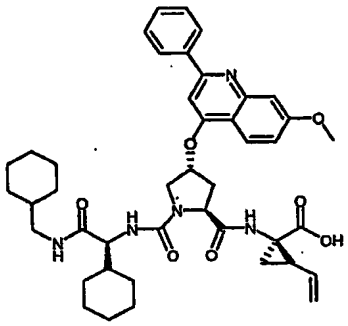
Example 74



(1R,2S)-1-{[(2S,4R)-1-((1R)-2-Hydroxy-1-phenyl-ethylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (74)

Compound 62 was treated as described for the preparation of 63 but with the use of (R)-2-phenylglycinol instead of 2-amino-N-(2-hydroxyindan-1-yl)-3,3-dimethyl butyramide instead of 2-amino-*N*-(2-hydroxy-indan-1-yl)-3,3-dimethyl-butyramide followed by ester hydrolysis as described for the preparation of compound 64 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 637.1.

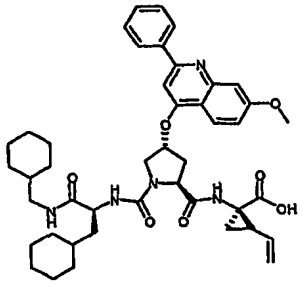
Example 75



(1R,2S)-1-{[(2S,4R)-1-{[(1S)-Cyclohexyl-(cyclohexylmethyl-carbamoyl)-methyl]-carbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (75)

N-(tert-butoxycarbonyl)-L-cyclohexylglycine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexanemethylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 752.4.

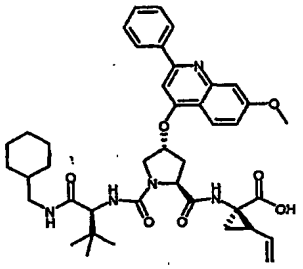
Example 76



(1R,2S)-1-{[(2S,4R)-1-[(1S)-2-Cyclohexyl-1-(cyclohexylmethyl-carbamoyl)-ethylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (76)

N-(tert-butoxycarbonyl)-L-cyclohexylalanine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexanemethylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 766.4.

Example 77

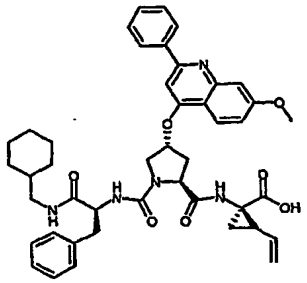


(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(Cyclohexylmethyl-carbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (77)

N-(tert-butoxycarbonyl)-L-tert-butylglycine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexanemethylamine as described for the preparation of 67 and removal of the Boc group as described for

68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 726.3.

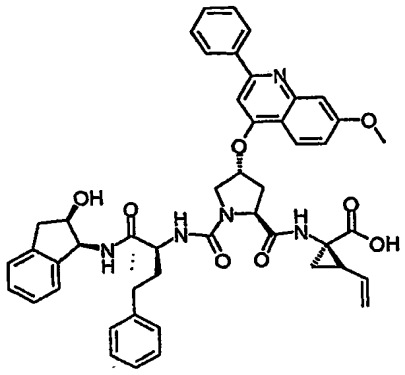
Example 78



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(Cyclohexylmethyl-carbamoyl)-2-phenyl-ethylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (78)

N-(tert-butoxycarbonyl)-L-phenylalanine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexanemethylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 760.4.

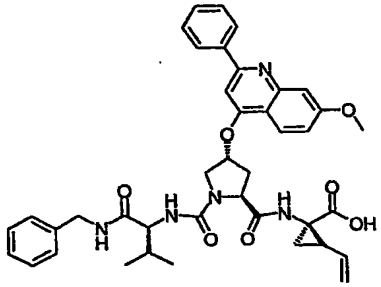
Example 79



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-((1S,2R)-2-Hydroxy-indan-1-ylcarbamoyl)-3-phenyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (79)

N-(tert.butoxycarbonyl)-L-phenethylglycine was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-cis-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 810.4.

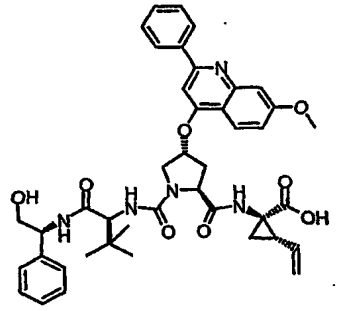
Example 80



(1R,2S)-1-{[(2S,4R)-1-((1S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (80)

N-(tert-butoxycarbonyl)-L-valine was attached to the resin as described for the preparation of compound 66 followed by reaction with benzylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. M+H$^+$ 706.2.

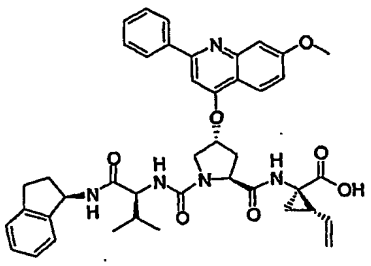
Example 81



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-((1R)-2-Hydroxy-1-phenyl-ethylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (81)

N-(tert-butoxycarbonyl)-L-tert-butylglycine was attached to the resin as described for the preparation of compound 66 followed by reaction with (R)-2-phenylglycinol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. M+H$^+$ 750.3.

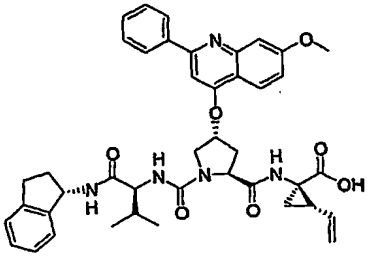
Example 82



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1R)-Indan-1-ylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (82)

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1R)-1-aminoindane as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (12.5 mg, 28 % yield), Purity by HPLC >90%. $M+H^+$ 732.2.

Example 83

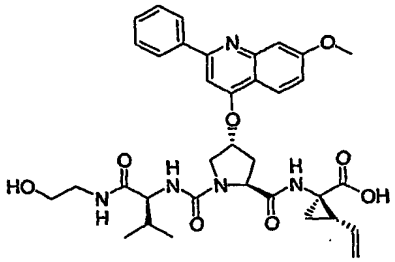


(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S)-Indan-1-ylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (83)

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S)-1-

aminoindane as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (22 mg, 49 % yield), Purity by HPLC >90% $M+H^+$ 732.2.

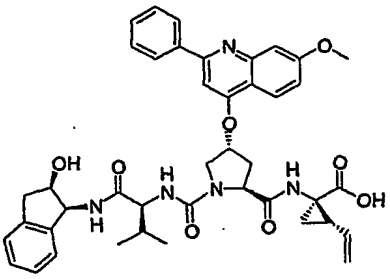
Example 84



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-(2-hydroxyethylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (84)

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with 2-aminoethanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (3 mg, 8 % yield), Purity by HPLC >90% $M+H^+$ 660.2.

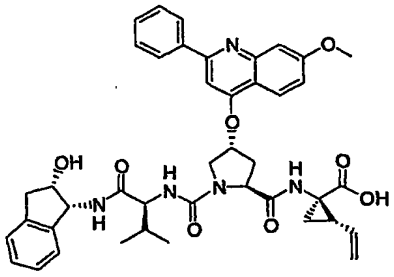
Example 85



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S, 2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (85)

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (10 mg, 22 % yield), Purity by HPLC >90% $M+H^+$ 748.2.

Example 86

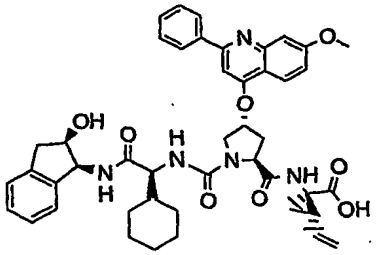


(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1R, 2S)-2-Hydroxy-indan-1-ylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (86)

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1R,2S)-1-

amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (11 mg, 24 % yield), Purity by HPLC >75% $M+H^+$ 748.

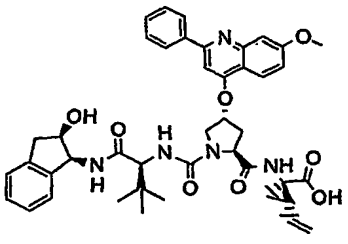
Example 87



(1R, 2S)-1-{[(2S, 4R)-1-{[Cyclohexyl-(S)-((1S, 2R)-2-hydroxy-indan-1-ylcarbamoyl)-methyl]-carbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (87)

(2S)-*tert*.butoxycarbonylamino-cyclohexylacetic acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (7.5 mg, 16 % yield), Purity by HPLC >95% $M+H^+$ 788.3.

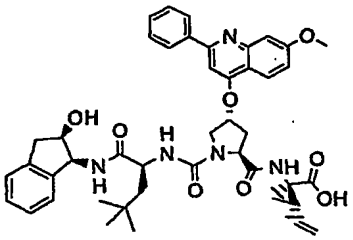
Example 88



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S, 2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2.2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (88)

(2S)-*tert*-butoxycarbonylamino-3,3-dimethylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (12 mg, 26 % yield), Purity by HPLC >95% $M+H^+$ 762.3.

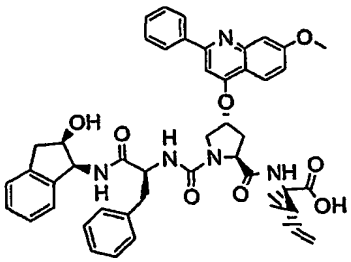
Example 89



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S, 2R)-2-Hydroxy-indan-1-ylcarbamoyl)-3,3-dimethyl-butylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (89)

(2S)-*tert*-butoxycarbonylamino-4,4-dimethylpentanoic acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (14.2 mg, 30 % yield), Purity by HPLC >95% $M+H^+$ 776.3.

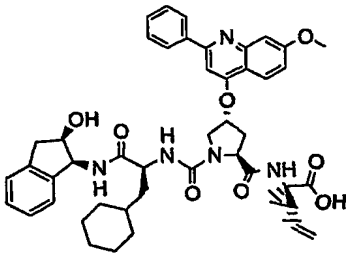
Example 90



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S, 2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2-phenyl-etylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (90)

(2S)-*tert*-butoxycarbonylamino-3-phenylpropanoic acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (2.4 mg, 5 % yield), Purity by HPLC >95% $M+H^+$ 796.2.

Example 91

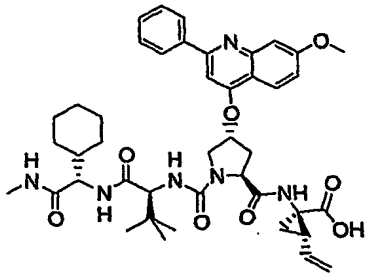


(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-2-Cyclohexyl-1-((1S, 2R)-2-hydroxy-indan-1-ylcarbamoyl)-ethylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (91)

(2S)-*tert*-Butoxycarbonylamino-3-cyclohexylpropanoic acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-

1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (12.3 mg, 25 % yield), Purity by HPLC >95% $M+H^+$ 802.3.

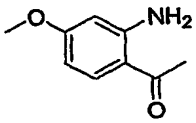
Example 92



(1R, 2S)-1-{[(2S, 4R)-1-{(1S)-1-[(S)-(Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (92)

Compound 62 was treated as described for the preparation of 63 but with the use of 71 instead of 2-amino-*N*-(2-hydroxy-indan-1-yl)-3,3-dimethyl-butyramide followed by ester hydrolysis as described for the preparation of compound 64 which, after purification by HPLC, gave the title compound(8.6 mg, 18 % yield). Purity by HPLC >95%. $M+H^+$ 783.3.

Example 93



1-(2-Amino-4-methoxyphenyl)ethanone (93)

*m*-Anisidine (10.0 g, 82 mmol) was dissolved in $CH_2Cl_2$ (50 mL), and the solution was cooled to -50 °C. $BCl_3$ (1 M in $CH_2Cl_2$, 82 mL, 82 mmol) was added slowly during 20 min, after which the mixture was stirred at -50 °C for 30 min, followed by sequential addition of AcCl (6.0 mL, 84 mmol) and $AlCl_3$ (11 g, 82 mmol). The mixture was stirred at -50 °C for 1 h and was then allowed to assume rt. After stirring at rt overnight, the solution was heated at 40 °C for 4 h, after which the mixture was poured over ice. The aqueous mixture was made alkaline with 10 % NaOH (w/v) and extracted with EtOAc (4 x 200 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated to give a black solid, which was purified by flash column chromatography (ether/$CH_2Cl_2$ 20:80). The resulting solid was recrystallized from ether/hexane to give compound 93 as shiny tan leaflets (5.6 g, 42 %).

Example 94

*N*-(*tert*-Butyl)-*N'*-isopropylthiourea (94)

To a solution of *tert*-butylisothiocyanate (5.0 mL, 39 mmol) in $CH_2Cl_2$ (200 mL) were added isopropylamine (4.0 mL, 47 mmol) and diisopropylethylamine (DIEA) (6.8 mL, 39 mmol), and the mixture was stirred at rt for 2h. The reaction mixture was diluted with EtOAc, washed with 10 % citric acid (2x), saturated $NaHCO_3$ (2x), $H_2O$ (2x), and brine (1x). The organic layer was dried ($MgSO_4$) and evaporated to yield compound 94 (3.3 g, 52 %) as a white solid which was used without further purification.

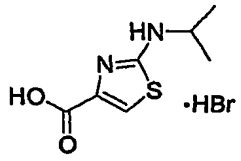
Example 95

*N*-Isopropylthiourea (95)

Compound 94 (3.3 g, 20 mmol) was dissolved in conc. HCl (45 mL) and the solution was refluxed for 40 min. The mixture was allowed to cool to rt and then cooled in an ice bath and basified to pH 9.5 with solid and saturated $NaHCO_3$, after which the product was extracted into EtOAc (3x). The combined organic phases were washed

with $H_2O$ (2x) and brine (1x), dried ($MgSO_4$), and evaporated to yield crude compound 95 (2.1 g, 90 %) which was used without further purification.

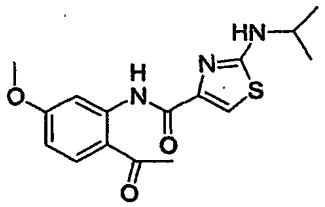
Example 96




2-(Isopropylamino)-1,3-thiazole-4-carboxylic acid hydrobromide (96)

A suspension of compound 95 (2.1 g, 18 mmol) and 3-bromopyruvic acid (3.0 g, 18 mmol) in dioxane (180 mL) was heated to 80°C. Upon reaching 80 °C the mixture became clear, and soon thereafter the product started to precipitate as a white solid. After 2 h of heating, the reaction mixture was cooled to rt and the precipitate was filtered off and collected. This yielded pure compound 96 (4.4 g, 94 %).

Example 97

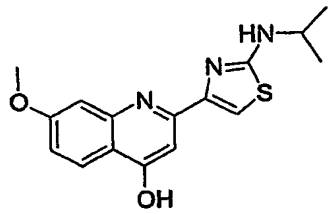



*N*-(2-Acetyl-5-methoxyphenyl)-2-(isopropylamino)-1,3-thiazole-4-carboxamide (97)

A mixture of compound 96 (4.4 g, 16.5 mmol) and the aniline derivative 93 (2.75 g, 16.5 mmol) in pyridine (140 mL) was cooled to -30 °C (upon cooling, the clear solution became partially a suspension). $POCl_3$ (3.3 mL, 35 mmol) was added slowly over a 5 min period. The mixture was stirred at -30 °C for 1 h, and was then allowed to assume rt. After stirring at rt for 1.5 h the reaction mixture was poured over ice, and the pH was adjusted to about 9-10 using solid and saturated $NaHCO_3$. The crude product was extracted into $CH_2Cl_2$ (3x) and the combined organic phases were dried ($MgSO_4$) and evaporated. The crude dark-beige solid was purified by flash

column chromatography (hexane/EtOAc 55:45) to give compound 97 (5.6 g, 76 %) as a pale yellow solid.

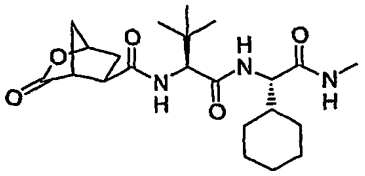
Example 98



2-[2-(Isopropylamino)-1,3-thiazol-4-yl]-7-methoxyquinolin-4-ol (98)

A solution of t.BuOK (2.42 g, 21 mmol) in anhydrous t.BuOH (40 mL) was heated to reflux. Compound 97 (1.8 g, 5.4 mmol) was added portion-wise over a 5 min period, and the dark red solution formed was stirred at reflux for an additional 20 min. The mixture was cooled to rt, and HCl (4 M in dioxane, 8.0 mL, 32 mmol) was added, after which the reaction mixture was concentrated under vacuum. In order to assure that all of the HCl and dioxane were removed, the crude product was re-dissolved in $CH_2Cl_2$ twice and thoroughly evaporated to obtain the slightly impure HCl salt of compound 98 (1.62 g) as a brown solid. The product was dissolved in $CH_2Cl_2$ and washed with saturated $NaHCO_3$, after which the aqueous phase was extracted several times with $CH_2Cl_2$. The combined organic phases were dried ($MgSO_4$) and evaporated to give compound 98 (1.38 g, 81 %) as a light brown solid (> 95 % pure according to HPLC tests). $^1$H-NMR (MeOH-$d_4$, 400 MHz): $\delta$ 1.30 (d, $J$ = 6.0 Hz, 6H), 3.93 (s, 3H), 3.95-4.07 (m, 1H), 6.73 (s, 1H), 6.99 (dd, $J$ = 2.4, 9.2 Hz, 1H), 7.26 (d, $J$ = 2.4 Hz, 1H), 7.37 (s, 1H), 8.10 (d, $J$ = 9.2 Hz, 1H).

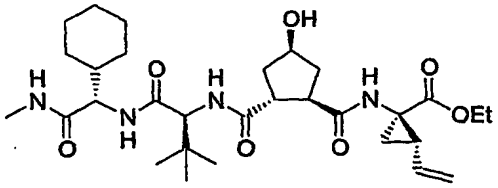
Example 99



(1*R*,4*R*,5*R*)-*N*-[(1*S*)-1-[[[(1*S*)-1-Cyclohexyl-2-(methylamino)-2-oxoethyl]amino]carbonyl]-2,2-dimethylpropyl]-3-oxo-2-oxabicyclo[2.2.1]heptane-5-carboxamide (99)

To a solution of compound 32 (53 mg, 0.34 mmol) in DMF (9 mL) was added compound 71 (80 mg, 0.28 mmol) and DIEA (290 µL, 1.66 mmol). The solution was cooled to 0 °C and HATU (127 mg, 0.33 mmol) was added. After stirring at 0 °C for 1 h and at rt for 1 h the solvent was evaporated, and the crude product was purified by flash column chromatography (EtOAc/toluene 2:1) to give compound 99 (110 mg, 92 %) as a white solid.

Example 100

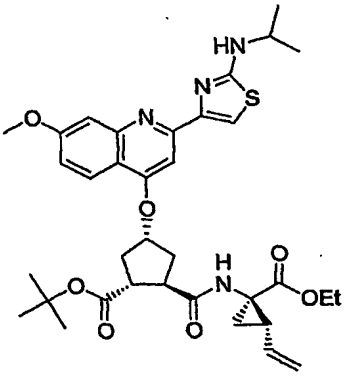


(1*R*)-1-[[[(1*R*,2*R*,4*R*)-2-[[[(1*S*)-1-[[[(1*S*)-1-Cyclohexyl-2-(methylamino)-2-oxoethyl]amino]carbonyl]-2,2-dimethylpropyl]amino]carbonyl]-4-hydroxycyclopentyl]carbonyl]amino]-2-ethenyl-cyclopropanecarboxylic acid ethyl ester (100)

Compound 99 (60 mg, 0.14 mmol) was dissolved in dioxane (3.5 mL) and $H_2O$ (2.5 mL) and the solution was cooled to 0 °C. LiOH (1 M, 280 µL, 0.28 mmol) was added dropwise during 5 min, after which the reaction mixture was stirred at 0 °C for 40 min. The pH was adjusted to 7 using 1 M HCl, and the solvents were evaporated. The residue was suspended in DMF (5 mL) and 1-amino-2-vinyl-

cyclopropanecarboxylic acid ethyl ester (32 mg, 0.17 mmol), and DIEA (146 µL, 0.84 mmol) were added. After cooling to 0 °C HATU (64 mg, 0.17 mmol) was added and the mixture was stirred at 0 °C for 1 h and at rt for 1 h. The solvent was evaporated and the product was purified using flash column chromatography (EtOAc/MeOH 9:1) to give compound 100 (67 mg, 82 %) as a white solid.

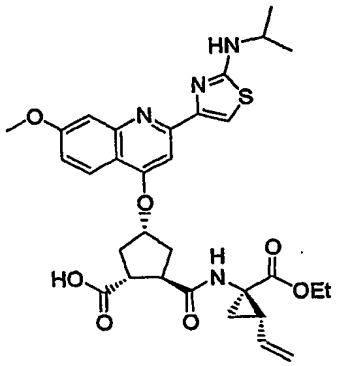
Example 101



*tert*-Butyl (1*R*,2*R*,4*R*)-2-[[[(1*R*)-1-(ethoxycarbonyl)-2-vinylcyclopropyl]amino]carbonyl]-4-[[2-[2-(isopropylamino)-1,3-thiazol-4-yl]-7-methoxyquinolin-4-yl]oxy]cyclopentanecarboxylate (101)

The title compound was prepared according to the procedure described in example 103 method A but with the use of compound 34 instead of compound 100. (Note: 4 equivalents of $Ph_3P$ and DIAD were used. Chromatography eluent: Toluene/EtOAc 1:1.)

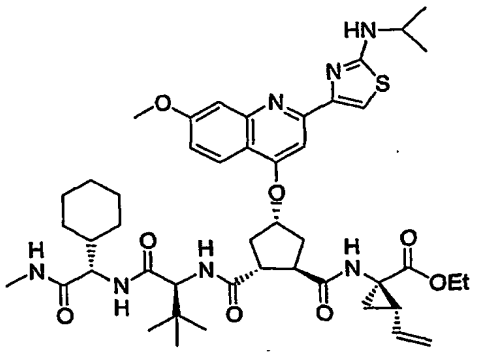
Example 102



(1*R*,2*R*,4*R*)-2-[[[(1*R*)-1-(Ethoxycarbonyl)-2-vinylcyclopropyl]amino]carbonyl]-4-[[2-[2-(isopropylamino)-1,3-thiazol-4-yl]-7-methoxyquinolin-4-yl]oxy]cyclopentanecarboxylic acid (102)

To a solution of compound 101 (20 mg, 30 μmol) in $CH_2Cl_2$ (2 mL) was added TFA (2 mL) and $Et_3SiH$ (10 μL, 63 μmol). After 2 h the volatiles were evaporated and the product was used without any purification step. Compound 102: 18 mg, quant. as a white solid.

Example 103

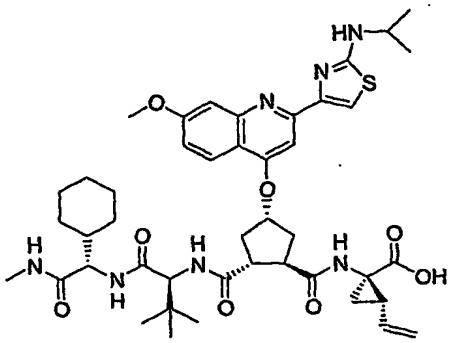


(1*R*)-1-[[[(1*R*,2*R*,4*S*)-2-[[[(1*S*)-1-[[[(1*S*)-1-Cyclohexyl-2-(methylamino)-2-oxoethyl]amino]carbonyl]-2,2-dimethylpropyl]amino]carbonyl]-4-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]cyclopentyl]carbonyl]amino]-2-ethenyl-cyclopropanecarboxylic acid ethyl ester (103)

Method A: To a solution of compound 100 (59 mg, 0.10 mmol) in dry THF (4 mL) was added the quinoline 98 (49 mg, 0.16 mmol) and $Ph_3P$ (65 mg, 0.25 mmol). After cooling to 0 °C DIAD (50 µL, 0.25 mmol) was added dropwise during 5 min. The solution was stirred at 0 °C for 1 h and at rt for 48 h. The solvent was evaporated and the remainder was purified using flash column chromatography ($CHCl_3$/2 M $NH_3$ in MeOH 95:5) to give compound 103 (9 mg, 10 %) as a white solid.

Method B: Compound 102 was coupled to compound 71 according to the procedure in example 99 which gave the title compound (82%).

Example 104

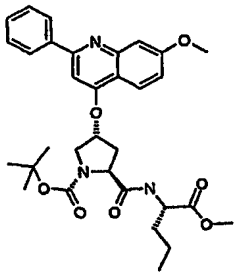


(1*R*)-1-[[[(1*R*,2*R*,4*S*)-2-[[[(1*S*)-1-[[[(1*S*)-1-Cyclohexyl-2-(methylamino)-2-oxoethyl]amino]carbonyl]-2,2-dimethylpropyl]amino]carbonyl]-4-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]cyclopentyl]carbonyl]amino]-2-ethenyl-cyclopropanecarboxylic acid (104)

Compound 103 (8 mg, 9 µmol) was dissolved in a mixture of MeOH (150 µL) and THF (100 µL). A solution of LiOH (1 mg, 42 µmol) in $H_2O$ (25µL) was added and the mixture was stirred at 50 °C overnight. The solution was neutralized with HOAc and evaporated. The residue was suspended in $CH_2Cl_2$ and washed with $H_2O$. The organic phase was evaporated to give the title compound (8 mg, quant.) as a white solid.

$^1$H-NMR (MeOH-$d_4$, 400 MHz) (mixture of rotamers): δ 0.60-1.33 (m, 21H), 1.35-1.73 (m, 12H), 1.90-2.42 (m, 2H), 2.51-2.75 (m, 6H), 3.20-3.38 (m, 1H), 3.85 (s, 3H), 3.95-4.28 (m, 1H), 4.91-5.02 (m, 1H), 5.12-5.23 (m, 1H), 5.64-5.83 (m, 1H), 7.01-7.11 (m, 1H), 7.25-7.40 (m, 1H), 7.42-7.57 (m, 1H), 7.85-8.08 (m, 1H).

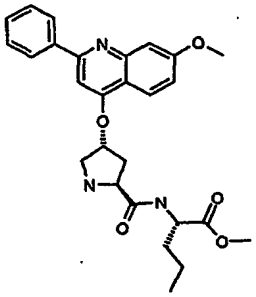
Example 105



(1S)-1-{[(2S,4R)-2-(1-Methoxycarbonyl-butylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy) ]-pyrrolidine}-carboxylic acid tert-butyl ester (105)

Reaction of 60 with Nva-OMe hydrochloride according to the method described in example 61 provided the title compound. Purity > 95% by HPLC, M+H$^+$ 578.24.

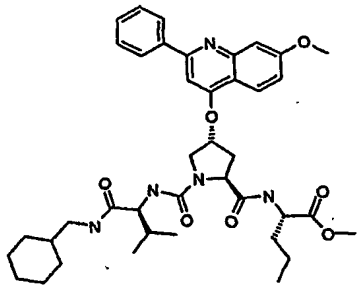
Example 106



(1S)-1-{[(2S,4R)-2-[4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-pentanoic acid methyl ester (106)

Compound 105 from above was kept in TFA-DCM 1:2 (3 mL) at RT for 60 min. Toluene (3 mL) was added. The sample was co-evaporated to dryness. Purity by HPLC > 95%. M+H$^+$ 478.21.

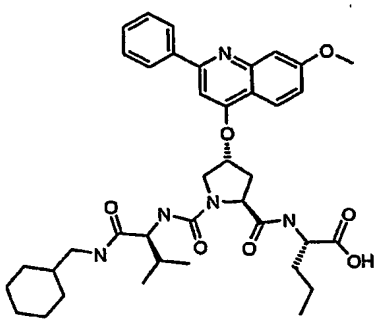
Example 107



(1S)-2-{[(2S,4R)-1-[(1S)-1-(Cyclohexylmethyl-carbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-pentanoic acid methyl ester (107)

To a solution of 106 (0.1 mmol) in THF (4 mL), cooled to 0 °C, was added a large excess of $NaHCO_3$ (s) and a solution of phosgene in toluene (0.2 mmol, 21μL). After 10 min of agitation the slurry was filtered and concentrated to dryness. The solid was redissolved in dichloromethane and a large excess of $NaHCO_3$ (s) and 2-amino-N-cyclohexylmethyl-3-methyl-butyramide, described in example 73, (0.15 mmol) was added. The slurry was agitated 30 hrs at RT. The slurry was filtered, concentrated and subjected to silica column chromatography (gradient elution from 100 % DCM to MeOH/DCM 2:98) to give the title compound (30 mg, 0.042 mmol). Purity by HPLC > 95%. M+H$^+$ 716.40.

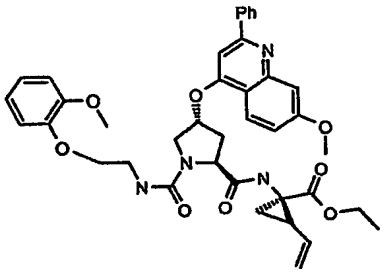
Example 108



(1S)-2-{[(2S,4R)-1-[(1S)-1-(Cyclohexylmethyl-carbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-pentanoic acid (108)

To a solution of 107 (26 mg, 0.036 mmol) in THF-MeOH 2:3 (2 mL) was added 1M LiOH 1.5 equiv. The solution was kept at 60 °C for 60 min. After cooling to RT, HOAc was added followed by toluene (2 mL) and then concentrated to dryness to give the title compound (25 mg, 0.035 mmol). Purity > 95% by HPLC $M+H^+$ 702.34.

Example 109

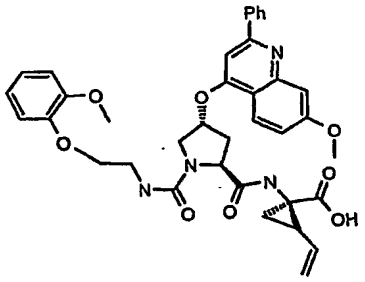


(1R,2S)-1-{[(2S,4R)-1-[2-(2-Methoxy-phenoxy)-ethylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (109)

To a solution of 62 (0.06 mmol) in THF (2 mL), was added a large excess of $NaHCO_3$ (s) and a solution of phosgene in toluene (0.078 mmol). After 10 min of agitation the slurry was filtered and concentrated to dryness. The solid was redissolved in dichloromethane and a large excess of $NaHCO_3$ (s) and 2-(2-

methoxy-phenoxy)-ethylamine (15 mg, 0.09 mmol) was added. The slurry was agitated for 30 hrs at RT. The slurry was filtered, concentrated to dryness, redissolved in MeOH and subjected HPLC purification to give the title compound (10.6 mg, 0.015 mmol). Purity by HPLC > 95%. $M+H^+$ 695.17.

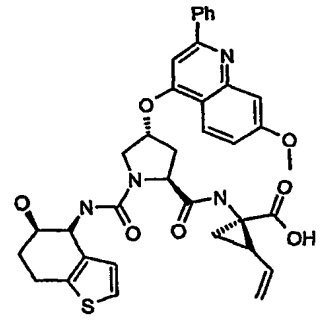
Example 110




(1R,2S)-1-{[(2S,4R)-1-[2-(2-Methoxy-phenoxy)-ethylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (110)

To a solution of 109 (10.6 mg, 0.0153 mmol) in THF-MeOH 2:3 (2 mL) was added 1M LiOH 10 equiv. The solution was kept at 50 °C for 60 min. After cooling to RT, HOAc 25 equiv. was added followed by toluene (2 mL) and then concentrated to dryness. The residue was taken up in ethyl acetate, filtered and concentrated to dryness to give the title compound (9.4 mg, 0.014 mmol). Purity > 95% by HPLC $M+H^+$ 667.14.

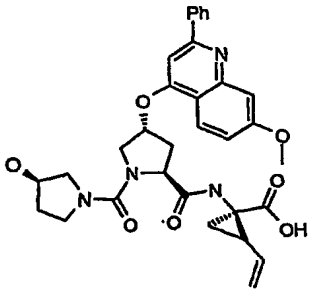
Example 111



(1R,2S)-1-{[(2S,4R)-1-((1S,2R)-5-Hydroxy-4,5,6,7-tetrahydro-benzo[b]thiophen-4-yl-carbamoyl))-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (111)

The procedure described in example 109 was followed but with the use of 2-amino-4,5,6,7-tetrahydro-benzo[b]thiophen-5-ol instead of 2-(2-methoxy-phenoxy)-ethylamine, followed by hydrolysis of the ethyl ester as described in example 110 which gave the title compound (7.5 mg, 0.011 mmol). Purity > 95% by HPLC $M+H^+$ 669.

Example 112

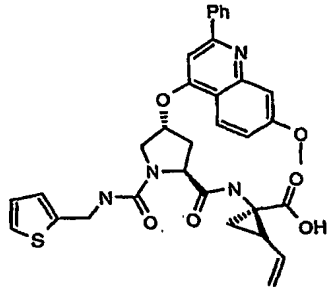


(1R,2S)-1-{[(2S,4R)-1-[(3R)-3-Hydroxy-pyrrolidine-1-carbonyl)]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (112)

The procedure described in example 109 was followed but with the use of (R)-3-pyrrolidinol instead of 2-(2-methoxy-phenoxy)-ethylamine, followed by hydrolysis of

the ethyl ester as described in example 110 which gave the title compound (4 mg, 0.007 mmol). Purity > 95% by HPLC $M+H^+$ 587.1.

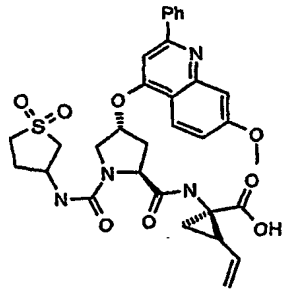
Example 113



(1R,2S)-1-{[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-1-[(thiophen-2-yl-methyl)-carbamoyl]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (113)

The procedure described in example 109 was followed but with the use of thiophene-2-methylamine instead of 2-(2-methoxy-phenoxy)-ethylamine, followed by hydrolysis of the ethyl ester as described in example 110 which gave the title compound (8 mg, 0.013 mmol). Purity > 95% by HPLC $M+H^+$ 613.08.

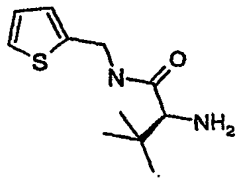
Example 114



(1R,2S)-1-{[(2S,4R)-1[(1,1-Dioxo-tetrahydro-1-$\lambda^6$-thiophen-3-yl -carbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (114)

The procedure described in example 109 was followed but with the use of 3-aminotetrahydro-1H-1$\lambda^6$-thiophene-1,1-dione instead of 2-(2-methoxy-phenoxy)-ethylamine, followed by hydrolysis of the ethyl ester as described in example 110 which gave the title compound (13 mg, 0.02 mmol). Purity > 95% by HPLC $M+H^+$ 635.05.

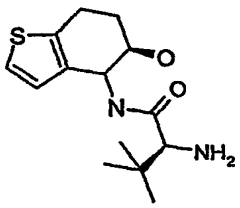
Example 115



2-Amino-3,3-dimethyl-N-thiophen-2-yl-methyl-butyramide (115)

The title compound was prepared as described in example 67 but with the use of thiophene-2-methylamine instead of aminoindanole followed by removal of the Boc group as described in example 68.

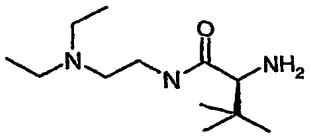
Example 116



2-Amino-N-(6-hydroxy-4,5,6,7-tetrahydro-benzo[b]thiophen-5-yl)-3,3-dimethyl-butyramide (116)

The title compound was prepared as described in example 67 but with the use of 2-amino-4,5,6,7-tetrahydro-benzo[b]thiophen-5-ol instead of aminoindanole followed by removal of the Boc group as described in example 68.

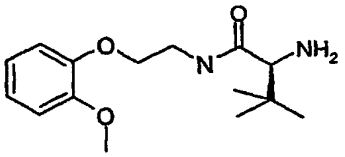
Example 117



2-Amino-N-(2-diethylamino-ethyl)-3,3-dimethyl-butyramide (117)

The title compound was prepared as described in example 67 but with the use of N,N-diethylethylenediamine instead of aminoindanole followed by removal of the Boc group as described in example 68.

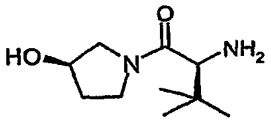
Example 118



2-Amino-N-[2-(2-methoxy-phenoxy)-ethyl]-3,3-dimethyl-butyramide (118)

The title compound was prepared as described in example 67 but with the use of 2-methoxyphenoxyethylamine instead of aminoindanole followed by removal of the Boc group as described in example 68.

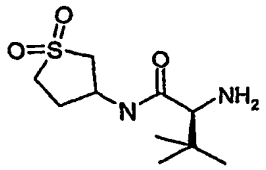
Example 119



2-Amino-1-(3-hydroxy-pyrrolidin-1-yl)-3,3-dimethyl-butan-1-one (119)

The title compound was prepared as described in example 67 but with the use of (R)-3-pyrrolidinone instead of aminoindanole followed by removal of the Boc group as described in example 68.

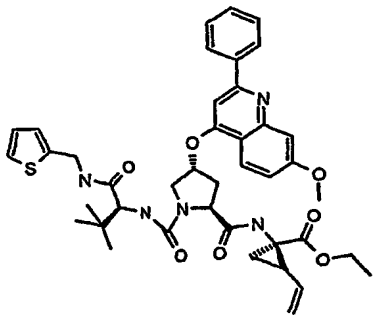
Example 120



2-Amino-N-(1,1-dioxo-tetrahydro-1-$\lambda^6$-thiophen-3-yl)-3,3-dimethyl-butyramide (120)

The title compound was prepared as described in example 67 but with the use of 2-methoxyphenoxyethylamine instead of aminoindanole followed by removal of the Boc group as described in example 68.

Example 121

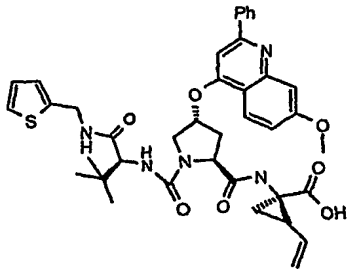


(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(2,2-Dimethyl-1-[(thiophen-2-yl-methyl)-carbamoyl]-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (121)

To a solution of 62 (0.06 mmol) in THF (2 mL), was added a large excess of $NaHCO_3$ (s) and a solution of phosgene in toluene (0.078 mmol). After 10 min of agitation the slurry was filtered and concentrated to dryness. The solid was redissolved in dichloromethane and a large excess of $NaHCO_3$ (s) and 115 (0.09 mmol) was added. The slurry was agitated for 30 hrs at RT. The slurry was filtered,

concentrated to dryness, re-dissolved in MeOH and subjected HPLC purification to give the title compound (15.5 mg, 0.02 mmol). Purity by HPLC > 95%. M+H$^+$ 754.2.

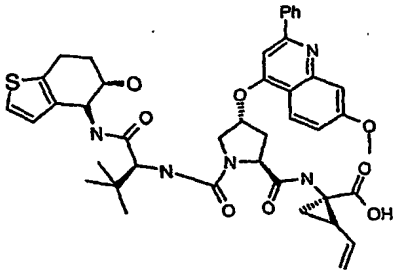
Example 122



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(2,2-Dimethyl-1-[(thiophen-2-ylmethyl)-carbamoyl]-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (122)

To a solution of 121 (14 mg, 0.017 mmol) in THF-MeOH 2:3 (2 mL) was added 1M LiOH 10 equiv. The solution was kept at 50 °C for 60 min. After cooling to RT, HOAc 20 equiv. was added followed by toluene (2 mL) and then concentrated to dryness. The residue was taken up in ethyl acetate, filtered and concentrated to dryness to give the title compound (13 mg, 0.017 mmol). Purity > 95% by HPLC M+H$^+$ 748.13.

Example 123

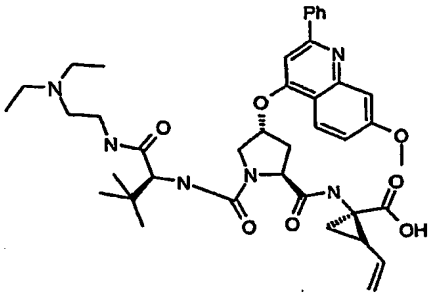


(1R,2S)-1-{[(2S,4R)-(1S)-1-[(1S,2R)-1-[1-(5-Hydroxy-4,5,6,7-tetrahydro-benzo[b]thiophen-4-yl-carbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-

phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (123)

The procedure described in example 121 was followed but with the use of 116 instead of 115, followed by hydrolysis of the ethyl ester as described in example 122 which gave the title compound (4 mg, 0.005 mmol). Purity > 95% by HPLC $M+H^+$ 782.16.

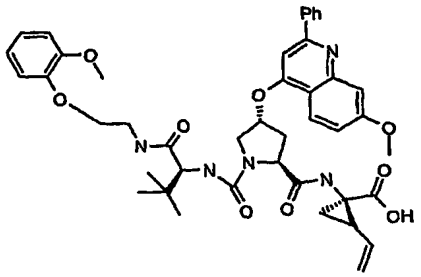
Example 124




(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(2-Diethylamino-ethylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (124)

The procedure described in example 121 was followed but with the use of 117 instead of 115, followed by hydrolysis of the ethyl ester as described in example 122 which gave the title compound (6 mg, 0.008 mmol). Purity > 95% by HPLC $M+H^+$ 729.24.

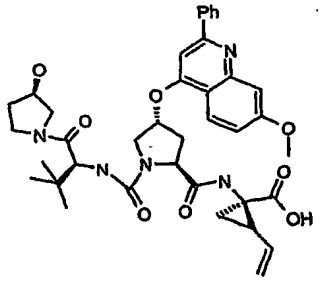
Example 125



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-[2-(2-Methoxy-phenoxy)-ethylcarbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (125)

The procedure described in example 121 was followed but with the use of 118 instead of 115, followed by hydrolysis of the ethyl ester as described in example 122 which gave the title compound (3 mg, 0.004 mmol). Purity > 95% by HPLC $M+H^+$ 780.19.

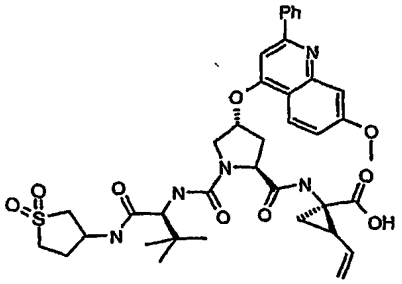
Example 126



(1R,2S)-1-{[(2S,4R)-(1S)-1-[(3R)-1-(3-Hydroxy-pyrrolidine-1-carbonyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (126)

The procedure described in example 121 was followed but with the use of 119 instead of 115, followed by hydrolysis of the ethyl ester as described in example 122 which gave the title compound (12.4 mg, 0.02 mmol). Purity > 95% by HPLC $M+H^+$ 700.16.

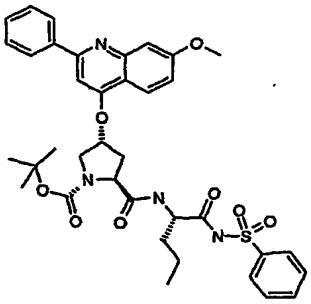
Example 127



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(1,1-Dioxo-tetrahydro-1-$\lambda^6$-thiophen -3-yl-carbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (127)

The procedure described in example 121 was followed but with the use of 120 instead of 115, followed by hydrolysis of the ethyl ester as described in example 122 which gave the title compound (13 mg, 0.014 mmol). Purity > 95% by HPLC M+H$^+$ 748.13.

Example 128

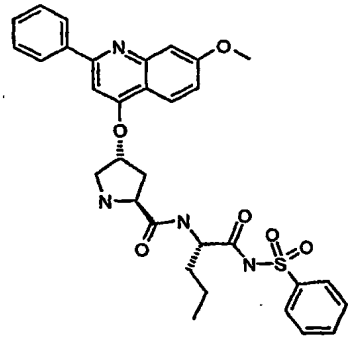


(4*R*)-1-(*tert*-butoxycarbonyl)-4-[(7-methoxy-2-phenylquinolin-4-yl)oxy]-L-prolyl-*N*$^1$-(phenylsulfonyl)-L-norvalinamide (128)

To a solution of 60 (60 mg, 0.13 mmol) in DMF, HATU (124 mg, 0.325 mmol), diisopropylethylamine (114 µL, 0.65 mmol) was added and agitated for 30 min at RT.

A solution of 131 (0.157 mmol) in DMF was added. The slurry was agitated for 16 hrs at RT followed by concentration to dryness. The residue was taken up in DCM and washed with $NaHCO_3$ (sat.), and water. The organic layer was dried, concentrated and subjected to silica column chromatography (gradient elution from 100% DCM to 2%MeOH/DCM) to give the title compound (61 mg, 0.087mmol). Purity > 90% by HPLC. $M+H^+$ 703.23.

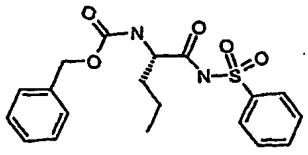
Example 129



(4*R*)-4-[(7-methoxy-2-phenylquinolin-4-yl)oxy]-L-prolyl-*N*$^1$-(phenylsulfonyl)-L-norvalinamide (129)

Compound 128 from above was kept in DCM-TFA 2:1 (2 mL) for 2.5 hr at RT. The solution was co-evaporated with toluene to dryness. Yield 100%. M+H 603.12

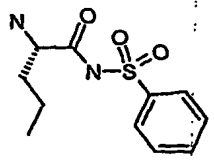
Example 130



Carbamic acid, [(1*S*)-1-[[(phenylsulfonyl)amino]carbonyl]butyl]-, phenylmethyl ester (130)

To a stirred solution of Z-Nva-OH (150 mg, 0.59 mmol) in THF (6 mL), CDI (400 mg, 2.4 mmol) was added. The slurry was agitated for 30 min at RT followed by the addition of DBU ( 200 µL, 1.3 mmol) and a solution of benzenesulfonamide (250 mg, 1.59 mmol) in THF(2 mL). The mixture was stirred at 60 °C for 48 hrs followed by concentration to dryness. The residue was dissolved in MeOH and subjected to HPLC purification to give the title compound (118.5 mg, 0.304 mmol). Purity > 95% by HPLC. M-H$^+$ 389.0, +Na 412.96.

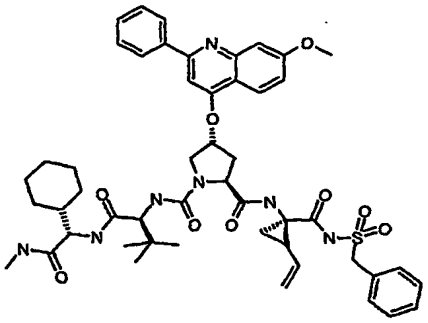
Example 131



(2S)-2-Amino-N-(phenylsulphonyl)pentanamide (131)

Compound 130 from above was dissolved in MeOH (5 mL) followed by the addition of Pd/C and subjected to hydrogenation for 2 hrs. The slurry was filtered through celite, washed with MeOH and concentrated to dryness to give the title compound. Yield 100%. M+H$^+$ 257.3.

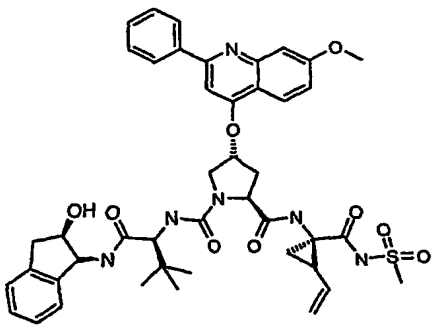
Example 132



4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-({1-[(cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-amide)-2-[(1-phenylmethanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-amide] (132)

To solution of 92 (8.7 mg, 0.011 mmol) in chloroform (1mL) was added α-toluenesulfonamide (7 mg, 0.04 mmol) followed by diisopropylethylamine (21 μL, 0.12 mmol). The solution was stirred at RT for 10 min and then at -20 °C for 30 min. PyBOP (46.5 mg, 0.08 mmol) was then added as a solid. The solution was kept at -20 °C for 48 hours. The solution was then poured into aqueous $NaHCO_3$ (sat.) and washed with water. The organic layer was dried, concentrated and subjected to purification by HPLC, affording the title compound as a white solid (2.8 mg, 0.0049 mmol), Purity by HPLC > 95%, $M+H^+$ 936.26.

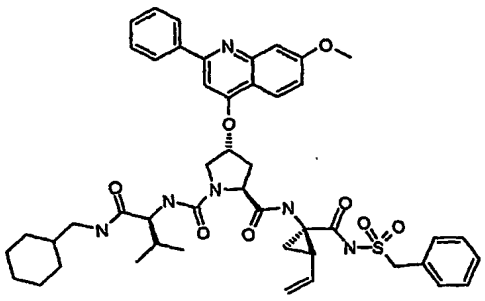
Example 133



N-(2-Hydroxy-indan-1-yl)-2-[4-(6-methoxy-3-phenyl-naphthalen-1-yloxy)-2-(1-methanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-pyrrolidin-1-yl]-3,3-dimethyl-butyramide (133)

The title compound was prepared as described in example 132, using 64 as carboxylic acid starting material and methanesulfonamide instead of α-toluenesulfonamide. Yield 13%, Purity by HPLC > 95%, $M+H^+$ 839.16.

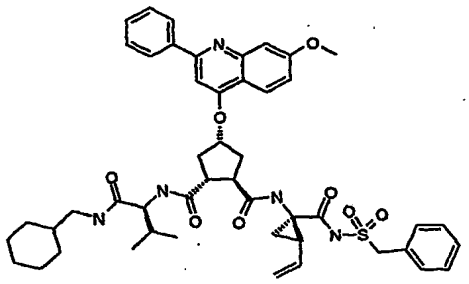
Example 134



4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-{[1-(cyclohexylmethyl-carbamoyl)-2-methyl-propyl]-amide} 2-[(1-phenylmethanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-amide] (134)

The title compound was prepared as described in example 132, using 73 as carboxylic acid starting material. Yield 2%. Purity > 95% by HPLC. $M+H^+$ 865.28.

Example 135

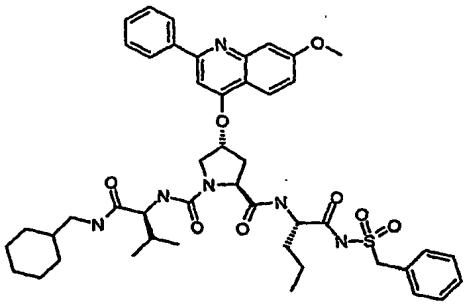


4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentane-1,2-dicarboxylic acid 1-{[1-(cyclohexylmethyl-carbamoyl)-2-methyl-propyl]-amide} 2-[(1-phenylmethanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-amide] (135)

N-(tert-Butoxycarbonyl)-L-valine was attached to Argonaut resin PS-TFP as described in example 66 followed by reaction with cyclohexanemethylamine as described in example 67 and removal of the Boc group as described in example 68. The afforded amine was used in a coupling reaction with compound 35 as described

in example 39 followed by hydrolysis of the ethyl ester as described in example 40 which gave 1-{[2-[1-(cyclohexylmethyl-carbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid. Reaction of this acid with α-toluenesulphonamide as described in example 132 gave the title compound. Yield 6%. Purity > 95% by HPLC. $M+H^+$ 864.32.

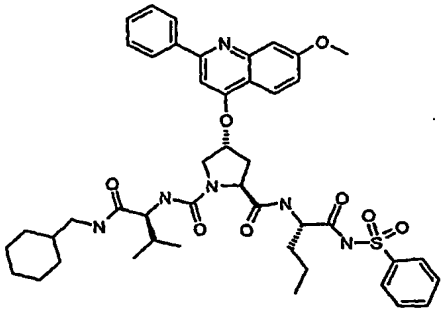
Example 136



4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-{[1-(cyclohexylmethyl-carbamoyl)-2-methyl-propyl]-amide} 2-[(1-phenylmethanesulfonylaminocarbonyl-butyl)-amide] (136)

The title compound was prepared as described in example 132, using 108 as carboxylic acid starting material. Yield 8%. Purity > 95% by HPLC. $M+H^+$ 855.28.

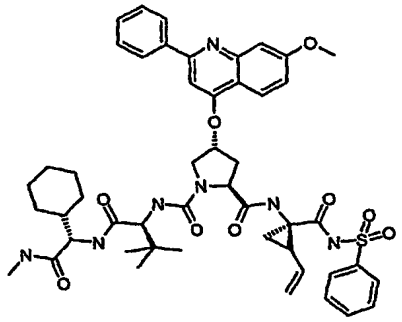
Example 137



4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 2-[(1-benzenesulfonylaminocarbonyl-butyl)-amide] 1-{[1-(cyclohexylmethyl-carbamoyl)-2-methyl-propyl]-amide} (137)

The title compound was prepared as described in example 132, using 108 as carboxylic acid starting material and benzensulpnonamide instead of α-toluenesulfonamide. Yield 21.5%. Purity > 95% by HPLC. $M+H^+$ 841.28.

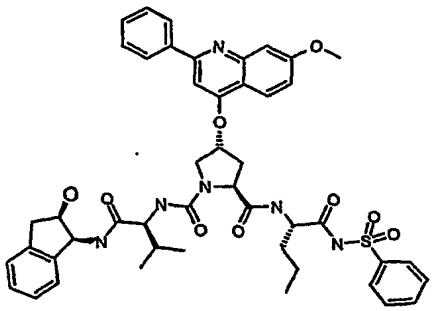
Example 138



4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 2-[(1-benzenesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-amide] 1-({1-[(cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-amide) (138)

The title compound was prepared as described in example 132, using benzenesulfonamide instead of α-toluenesulfonamide. Yield 26 %. Purity by HPLC > 95 %, $M+H^+$ 922.23.

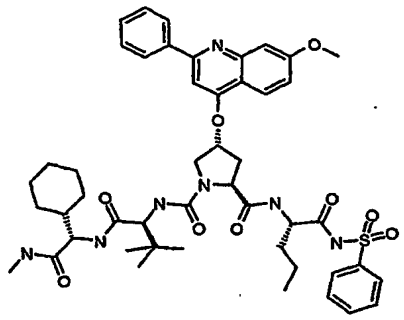
Example 139



4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 2-[(1-benzenesulfonylaminocarbonyl-butyl)-amide] 1-{[1-(2-hydroxy-indan-1-ylcarbamoyl)-2-methyl-propyl]-amide} (139)

To a solution of 129 (24.1 mg, 0.04 mmol) in DCM (2 mL), was added a large excess of $NaHCO_3$ (s) and a solution of phosgene in toluene (50 µL, 0.096 mmol). After 10 min of agitation the slurry was filtered and concentrated to dryness. The solid was redissolved in DCM and a large excess of $NaHCO_3$ (s) and 2-amino-*N*-(2-hydroxy-indan-1-yl)-3-methyl-butyramide, described in example 85, (0.1 mmol) was added. The slurry was agitated for 40 hrs at RT. The slurry was filtered, concentrated and subjected to HPLC purification, to give the title compound (1.6 mg, 0.0018 mmol). Purity > 95% by HPLC. $M+H^+$ 877.21.

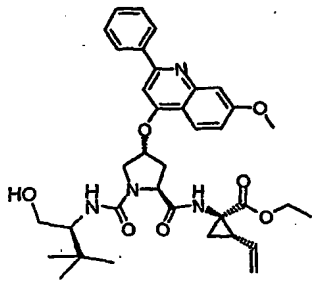
Example 140



4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 2-[(1-benzenesulfonylaminocarbonyl-butyl)-amide] 1-({1-[(cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-amide) (140)

The title compound was prepared as described in example 139 but using 71 instead of 2-amino-*N*-(2-hydroxy-indan-1-yl)-3-methyl-butyramide. Yield 2%. Purity > 95% by HPLC. M+H$^+$ 912.25.

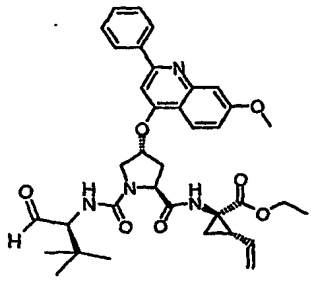
Example 141



(1R,2S)-1-{[(4R,2S)1-(1-(1S)-Hydroxymethyl-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (141)

Treatment of compound 62 as described for the preparation 63 but with the use of (S)-tert-leucinol instead of 2-amino-N-(2-hydoxy-indan-1-yl) 3,3-dimethyl-butyramide provided the title product. M+H$^+$ 645.2.

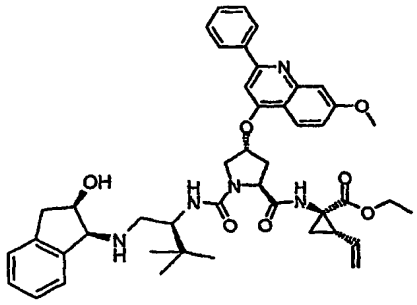
Example 142



(1R,2S)-1-{[(4R,2S)1-(1-(1S)-Formyl-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (142)

To a stirred solution of compound 141 (64 mg) in dichloromethane Dess-Martin periodinane (80 mg) was added at ambient temperature. After 4 hrs the slurry was filtered through basic alumina and concentrated to dryness. M+H$^+$ 643.2.

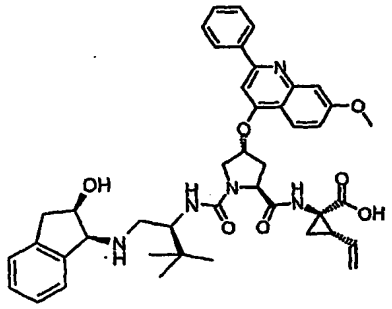
Example 143



(1R,2S)-1-{[(4R,2S)1-{1-[((1S,2R)-2-Hydroxy-indan-1-ylamino)-methyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (143)

To a solution of compound 142 in THF (2 mL) and HOAc (0.5 mL) polystyrene bound cyanoborohydride (2.36 mmol/g, 100 mg) and (1S,2R)-1-aminoindan-2-ol (18 mg) was added and agitated for 4 hrs. The mixture was filtered, concentrated and purified on a prep. HPLC. Purity by HPLC >90%. M+H$^+$ 776.5

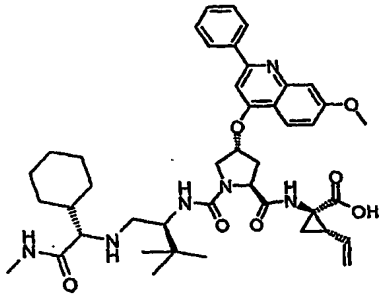
Example 144



(1R,2S)-1-{[(4R,2S)1-{1-[((1S,2R)-2-Hydroxy-indan-1-ylamino)-methyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (144)

To a solution of compound 143 in THF (2 mL) and MeOH (1 mL) 1N LiOH (0.2 mL) was added and the solution was kept at 60 °C for 1.5 hrs. The slurry was neutralized with 1N HCl to pH 7, concentrated and purified on a prep. HPLC giving pure product by HPLC >95%. $M+H^+$ 748.4.

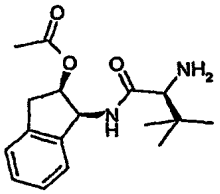
Example145



(1R,2S)-1-{[(4R,2S)1-(1-{[(1S)-(Cyclohexyl-methylcarbamoyl-methyl)-amino]-methyl}-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (145)

Treatment of compound 142 as described for the preparation of 143 but with the use of 2-amino-2-cyclohexyl-N-metyl-acetamide (17 mg) instead of (1S,2R)-1-aminoindan-2-ol followed by hydrolysis of the ethyl ester as described in example 144 provided the title product. Purity by HPLC >95%. $M+H^+$ 769.5

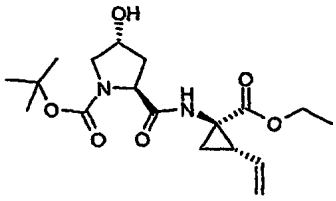
Example 146



Acetic acid (1S,2R)-1-((2S)-2-amino-3,3-dimethyl-butyrylamino)-indan-2-yl ester (146)

A solution of compound 67 (4g) was kept in pyridine-acetic anhydride 2:1 for 30 min. DCM was added and the solution was washed with citric acid (aq) and $NaHCO_3$ (aq). The organic layer was concentrated to dryness which gave the acetylated product >90% pure by HPLC. The afforded compound was then kept in a solution of 30% TFA in DCM for 1.5 hrs and then concentrated to dryness. Co-evaporation twice from toluene gave the title product >90% pure by HPLC.

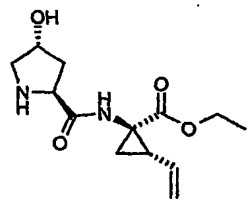
Example 147



(2S,4R)-2-((1S,2R)1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert.butyl ester (147)

A solution of HATU (6 g), diisopropylethylamine (6.8 mL), (1R,2S)-1-amino-2-vinyl-cyclopropanecarboxylic acid ethyl ester (1.5 g) and BOC-L-hydroxyproline (1.6 g) in dichloromethane was stirred for 1 hrs. The mixture was extracted with DCM-$NaHCO_3$ (aq) dried and concentrated. HPLC purity ca 90% $M+H^+$ 369.1.

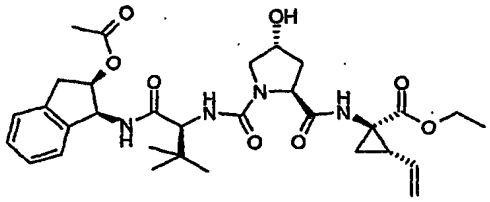
Example 148



(1S,2R)-1-[(2S,4R)-(4-Hydroxy-pyrrolidine-2-carbonyl)-amino]-2-vinyl-cyclopropanecarboxylic acid ethyl ester (148)

Compound 147 was kept in 30% trifluoroacetic acid in dichloromethane and 1% MeOH for 2 hrs before it was concentrated to dryness. The residue was re-dissolved in dichloromethane and during stirring 1N NaOH was added to pH 10-11. The organic layer was separated and concentrated which gave 1.6 g of the title product. HPLC purity ca. 90% $M+H^+$ 269.1.

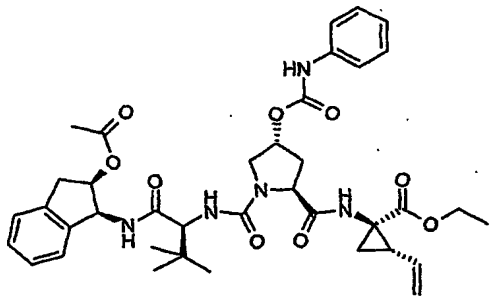
Example 149



(1R,2S)-1-({(2S,4R)-1-[(1S)-1-((1S,2R)-2-Acetoxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-hydroxy-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid ethyl ester (149)

To a stirred solution of compound 146 (1.81 g) in acetonitrile at 0 °C solid $NaHCO_3$ (800 mg) and p-nitrophenychlorocarbonate (1.2 g) was added. The slurry was taken up to ambient temperature and stirred for another 30 min. To this slurrry a slution of compound 148 (1.6 g) in acetonitrile (5 mL) diisopropylethylamine (1mL) was added. After 10 min the resulting mixture was concentrated, re-dissolved in ethyl acetate and washed with $K_2CO_3$ (aq) and then with 0.5 N HCl. Dried and concentrated which gave a >80% pure product by HPLC $M+H^+$ 599.6

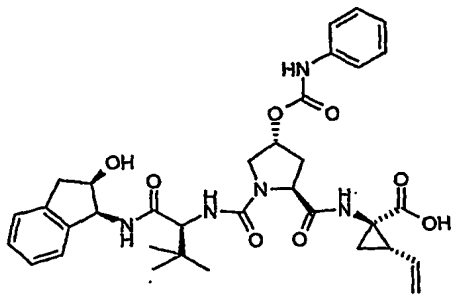
Example 150



(1R,2S)-1-({(2S,4R)-1-[(1)-1-((1S,2R)-2-Acetoxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-phenylcarbamoyloxy-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid ethyl ester (150)

To a stirred solution of compound 149 (20mg) in DCM and solid $K_2CO_3$ (200 mg) 20% phosgene in toluene (1 mL) was added. After 6 hrs the slurry was filtered and concentrated to dryness. To this residue a mixture of aniline (30 mg) DCM (3 mL) and solid $NaHCO_3$ (50 mg) was added and agitated for 10 hrs. The mixture was filtered, concentrated and purified on a prep. HPLC which gave the title product, >95% pure $M+H^+$ 718.6.

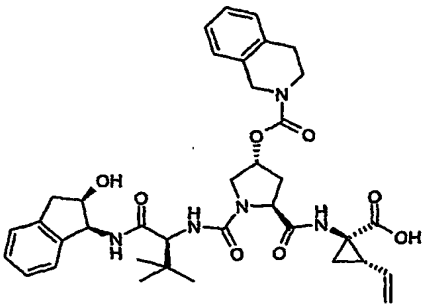
Example 151



(1R,2S)-1-({(2S,4R)-1-[1-((1S,2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-phenylcarbamoyloxy-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (151)

To a solution of compound 150 in THF-MeOH 2:1 (3 mL) was added 1N LiOH (0.2 mL). The solution was heated to 60 °C for 2 hrs. After cooling to ambient temperature acetic acid (0.5 mL) was added and the solution was concentrated to dryness. The remaining residue was purified on a prep. HPLC which gave the title product >95% pure M+H+ 648.5.

Example 152

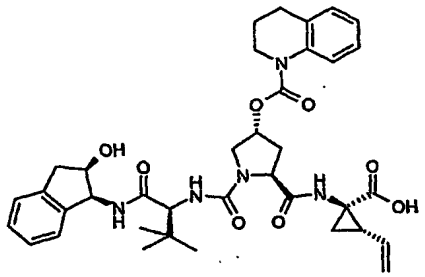


(5S,3R)-3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 5-((1R,2S)-1-carboxy-2-vinyl-cyclopropylcarbamoyl)-1-[1-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-pyrrolidin-3-yl ester (152)

Treatment of compound 149 as described for the preparation of 150 but with the use of 1,2,3,4-tetrahydro-isoquinoline instead of aniline followed by hydrolysis of the ethyl

ester as described in example 151 gave the title compound. Purity >90%. M+H$^+$ 688.6.

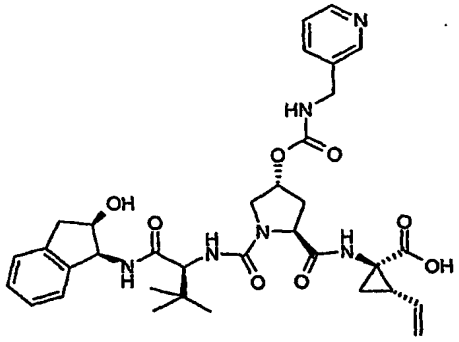
Example 153



(5S,3R)-3,4-Dihydro-2H-quinoline-1-carboxylic acid 5-((1R,2S)-1-carboxy-2-vinyl-cyclopropylcarbamoyl)-1-[1-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-pyrrolidin-3-yl ester (153)

Treatment of compound 149 as described for the preparation of 150 but with the use of 1,2,3,4-tetrahydro-quinoline instead of aniline followed by hydrolysis of the ethyl ester as described in example 151 gave the title compound. Purity >90%. M+H$^+$ 688.6.

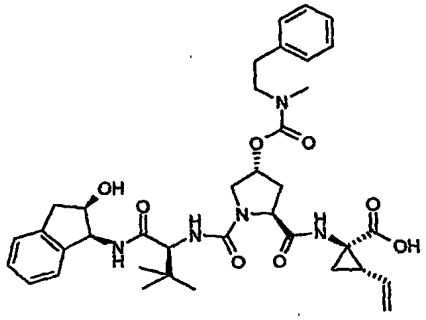
Example 154



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-((1S,2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(pyridin-3-ylmethylcarbamoyloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (154)

Treatment of compound 149 as described for the preparation of 150 but with the use of 2-pyridine-3-yl-ethylamine instead of aniline followed by hydrolysis of the ethyl ester as described in example 151 gave the title compound. Purity >90%. $M+H^+$ 663.5.

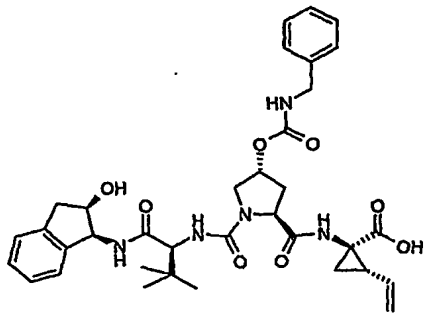
Example 155



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-((1S,2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(methyl-phenethyl-carbamoyloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (155)

Treatment of compound 149 as described for the preparation of 150 but with the use of N-methylphenthylamine instead of aniline followed by hydrolysis of the ethyl ester as described in example 151 gave the title compound. Purity >90%. $M+H^+$ 690.6.

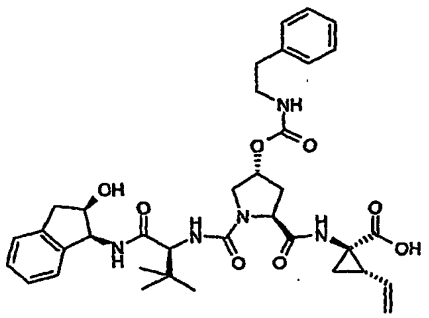
Example 156



(1R,2S)-1-({(2S,4R)-4-Benzylcarbamoyloxy-1-[(1S)-1-((1S,2R)-2-hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (156)

Treatment of compound 149 as described for the preparation of 150 but with the use of benzylamine instead of aniline followed by hydrolysis of the ethyl aster as described in example 151 gave the title compound. Purity >90%. $M+H^+$ 662.4.

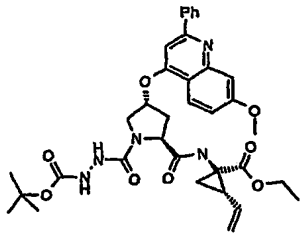
Example 157



(1R,2S)-1-({(2S,4R)-1-[(1S)-1-((1S,2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-phenethylcarbamoyloxy-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (157)

Treatment of compound 149 as described for the preparation of 150 but with the use of phenthylamine instead of aniline followed by hydrolysis of the ethyl aster as described in example 151 gave the title compound.Purity >90%. $M+H^+$ 676.5.

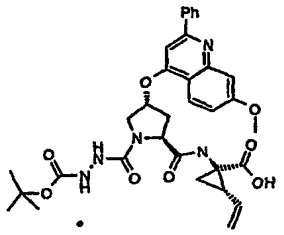
Example 158



(1*R*,2*S*)-1-({(4*R*)-1-{[2-(*tert*-butoxycarbonyl)hydrazino]carbonyl}-4-[(7-methoxy-2-phenylquinolin-4-yl)oxy]-L-prolyl}amino)-2-vinylcyclopropanecarboxylic acid ethyl ester (158)

To a solution of *tert*-butyl carbazate (0.3 mmol) and p-nitro phenyl chloroformate (0.3 mmol) in acetonitrile (6 mL) was added sodium hydrogen carbonate (0.48 mmol) as solid. The solution was stirred at RT for 5 hrs and then cooled down to 0 °C. Compound 62 (0.3 mmol) dissolved in acetonitrile (10 mL) was mixed together with diisopropylethylamine (0.75 mmol) at 0 °C, and then added to the previous solution. The mixture was stirred at RT overnight and then concentrated to dryness. The residue was dissolved in DCM and then washed with citric acid pH 4, followed by $NaHCO_3$ (aq) and water, dried over anhydrous sodium sulphate, filtrated and concentrated to dryness. The crude was dissolved in DCM and purified by column chromatography eluted with 0.1 to 0.2% MeOH/DCM to yield the title compound (101 mg). Purity >95% by HPLC, $M+H^+$ 660.1.

Example 159

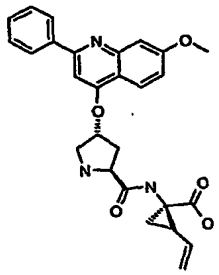


(1*R*,2*S*)-1-({(4*R*)-1-{[2-(*tert*-butoxycarbonyl)hydrazino]carbonyl}-4-[(7-methoxy-2-phenylquinolin-4-yl)oxy]-L-prolyl}amino)-2-vinylcyclopropanecarboxylic acid (159)

Method A: To a solution of compound 158 (0.0115 mmol) in THF-MeOH 2:3 (2 mL) was added 1M LiOH (10 equiv) The solution was kept at 50 °C for 60 min. After cooling to RT, HOAc (20 equiv) was added followed by toluene (2 mL) and then concentrated to dryness. The residue was taken up in MeOH and then purified by Prep LCMS which gave the title compound (0.7 mg). Purity >95% by HPLC $M+H^+$ 732.2.

Method B: To a solution of *tert*-butyl carbazate (0.07 mmol) and p-nitrophenyl chloroformate (0.07 mmol) in acetonitrile (3 mL) was added sodium hydrogen carbonate (0.112 mmol) as a solid. The solution was stirred at RT for 2.5 hrs and then cooled to 0 °C. Compound 160 (described below) (0.07 mmol) dissolved in acetonitrile (10 mL) was mixed together with diisopropylethylamine (0.175 mmol) at 0 °C, and then added to the previous solution. The mixture was stirred at RT overnight and then concentrated to dryness. The crude material was dissolved in MeOH and purified by Prep LCMS which gave the title compound (4.8 mg). Purity >95% by HPLC $M+H^+$ 632.2

Example 160

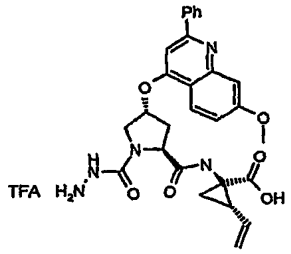


(1R,2S)-1-{[(2S,4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (160)

To a solution of compound 62 (0.067mmol) in THF-MeOH 2:3 (2 mL) was added 1M LiOH 10 equiv. The solution was kept at 50 °C for 2.5 hrs. After cooling to RT, HOAc

20 equiv. was added followed by toluene (2 mL) and then concentrated to dryness. The residue was taken up in DCM and filtered form the salts which gave the title compound (0.07 mmol). Purity >95% by HPLC $M+H^+$ 474.

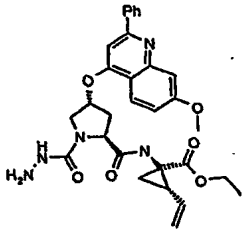
Example 161




(1*R*,2*S*)-1-({(4*R*)-1-(hydrazinocarbonyl)-4-[(7-methoxy-2-phenylquinolin-4-yl)oxy]-L-prolyl}amino)-2-vinylcyclopropanecarboxylic acid (161)

Compound (159) from above was kept in TFA-DCM 1:2 (3 mL) at RT for 60 min. Toluene (1 mL) was added. The sample was co-evaporated to dryness which gave the title compound (10.5 mg) as the trifluoracetic acid salt. Purity by HPLC >95%. $M+H^+$532.

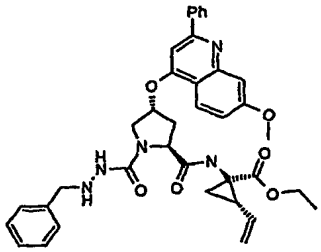
Example 162




(1*R*,2*S*)-1-({(4*R*)-1-(hydrazinocarbonyl)-4-[(7-methoxy-2-phenylquinolin-4-yl)oxy]-L-prolyl}amino)-2-vinylcyclopropanecarboxylic acid ethyl ester (162)

Compound 158 (50 mg) was kept in TFA-DCM 1:2 (3 mL) at RT for 60 min. Toluene (1 mL) was added. The sample was co-evaporated to dryness and then taken up in DCM and washed with $K_2CO_3$, dried over anhydrous sodium sulphate and concentrated to dryness which gave the title compound (41.8 mg). Purity by HPLC >95%. $M+H^+$ 560.

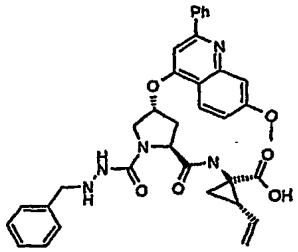
Example 163




(1*R*,2*S*)-1-({(4*R*)-1-[(2-Benzylhydrazino)carbonyl]-4-[(7-methoxy-2-phenylquinolin-4-yl)oxy]-L-prolyl}amino)-2-vinylcyclopropanecarboxylic acid etyl ester (163)

To a solution of compound 162 (0.037mmol) in MeOH:THF (4:1) was added benzaldehyde (0.0448 mmol). The solution was stirred at RT for 18 hrs. Borane-pyridine complex (0.37 mmol) was added followed by HCl (37%, 400 µl). The solution was stirred for 1.5 hrs and then filtrated and concentrated to dryness. The crude material was dissolved in MeOH and purified by Prep LCMS which gave the title compound (0.01 mmol). Purity by HPLC >95%. $M+H^+$ 650.

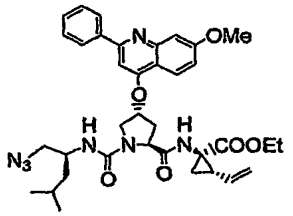
Example 164



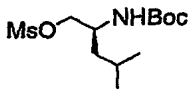
(1*R*,2*S*)-1-({(4*R*)-1-[(2-benzylhydrazino)carbonyl]-4-[(7-methoxy-2-phenylquinolin-4-yl)oxy]-L-prolyl}amino)-2-vinylcyclopropanecarboxylic acid (164)

To a solution compound 163 ( 0.0101 mmol) in THF-MeOH 2:3 (3 mL) was added 1M LiOH 10 equiv. The solution was kept at 50 °C for 18 hrs. After cooling to RT the sample was neutralized with HCl and concentrated to dryness. The crude material was dissolved in DCM (2 mL) and a solution of TFA: TES 1:1 (1 mL) was added. The mixture was stirred for 3 hrs at RT and then concentrated to dryness. The crude material was dissolved in MeOH and purified by Prep LCMS which gave the title compound (0.6 mg). Purity by HPLC >95%. $M+H^+$ 622.

Example 165

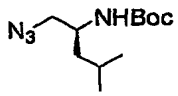


(1R, 2S)-1-{[(2S, 4R)-1-((1S)-1-Azidomethyl-3-methyl-butylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (165)



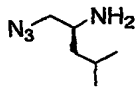
i) (2S)-Methanesulphonic acid 2-tert.butoxycarbonylamino-4-methyl-pentyl ester

To a solution of ((1S)-1-hydroxymethyl-3-methyl-butyl)-carbamic acid tert-butyl ester (25 g, 115 mmol) in dichloromethane (500 mL) cooled by an ice-water bath was successively added diisopropylethylamine (35.7 g, 276 mmol) and methanesulphonyl chloride (15.81 g, 138 mmol). The resulting solution was stirred over night during which time the mixture was allowed to gradually warm up to ambient temperature. The mixture was washed successively with water, 10 % citric acid (aq), water and saturated $NaHCO_3$ (aq), then dried with $Na_2SO_4$ and concentrated to a brown solid (32.6 g, 96 %) which was used in the next reaction without further purification.




ii) ((1S)-1-Azidomethyl-3-methyl-butyl)-carbamic acid tert.butyl ester

The mesylate from step i (32.6 g, 110 mmol) was treated with sodium azide (21.45 g, 330 mmol) in DMF at 80 °C for 24 hrs. The solvent was evaporated, the residue was taken up in DCM, filtered and washed with saturated $NaHCO_3$ (aq). The solution was dried with $Na_2SO_4$ and concentrated to a brown oil which was purified by flash chromatography using a gradient of ethyl acetate and hexane to afford the title compound as a white solid (19.55 g, 73 %).

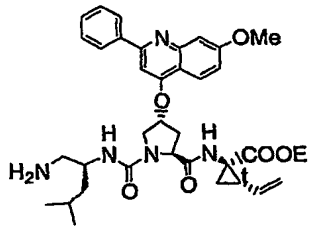



iii) (1S)-1-Azidomethyl-3-methyl-butylamine

((1S)-1-Azidomethyl-3-methyl-butyl)-carbamic acid tert-butyl ester (9.64 g, 39.78 mmol) was treated with TFA (30 mL) in DCM (150 mL) for 3 hrs, the mixture was evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed with aqueous 1 M $K_2CO_3$, dried with $Na_2SO_4$ and concentrated to a yellow liquid (4.55 g, 80 %).

Compound 62 was treated with phosgene as described in example 63 which gave the corresponding chlorocarbamate compound. The afforded chlorocarbamate (568 mg, 1.13 mmol) was dissolved in a solution of DCM-THF (1:1, 10 mL) and (1S)-1-azidomethyl-3-methyl-butylamine (401 mg, 2.82 mmol) and a large excess of $NaHCO_3$ (s) was added. The resulting mixture was stirred for 18 hrs, filtered and washed with dilute citric acid (aq, pH 5). The organic layer was dried with $Na_2SO_4$ and evaporated to afford the desired product as a light yellow oil (837 mg, 99 %) sufficiently pure to be used in the next step.
$M+H^+$ 670.1.

Example 166




(1R, 2S)-1-{[(2S, 4R)-1-((1S)-1-Aminomethyl-3-methyl-butylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (166)

A solution of 165 (717 mg, 1.07 mmol) in THF (25 mL) was shaken together with PS-triphenylphosphine resin (diphenylphosphino polystyrene) (3.24 g, 1.65 mmol $PPh_3$/g) and methanol (2.5 mL) for 78 hrs. The mixture was filtered and the polymer was washed repeatedly with DCM and methanol. The combined filtrates were evaporated to yield the title compound as a light beige solid foam (685 mg, 99 %) with more than 95 % purity as determined by reversed phase HPLC. $M+H^+$ 644.1.

General procedure 1A for the preparation of compounds 167-173

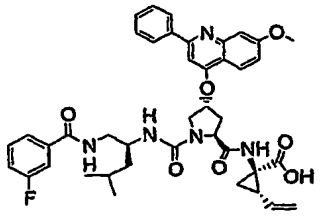
To a solution of the acyl chloride (0.075 mmol) in DCM (0.5 mL) was added $NaHCO_3$ (s) (60 mg, 07 mmol) and a solution of the amine 167 (25 mg, 0.037 mmol) in THF (1 mL). The resulting mixture was stirred at room temperature over night , filtered and

then shaken in the presence of PS-trisamine resin (tris-(2-aminoethyl) aminomethyl polystyrene) (3.91 mmol/ g, 50 mg, 0.2 mmol) for 5 hrs. The mixture was filtered and evaporated. The resulting solid residue was dissolved in MeOH-THF (2:1, 1.5 mL) and treated with 1 M LiOH (aq) (170 µl) at 50 °C between 2 and 16 hrs. The reaction was monitored by HPLC-MS. The mixture was acidified with acetic acid and evaporated to dryness. The residue was dissolved in methanol and purified by reversed phase HPLC.

General procedure 1B for the preparation of compounds 167-173

To the acid (0.039 mmol) was successively added a solution of HATU (14.7 mg, 0.039 mmol) in DMF (0.5 mL), a solution of the amine 166 (20 mg, 0.031 mmol) in DMF (0.5 mL) and diisopropylethylamine (30 µl, 0.155 mmol). The resulting mixture was stirred for 16 hrs then the solvent was evaporated and the residue was dissolved in DCM and washed with water and aqueous saturated $NaHCO_3$. The solvent was evaporated and the residue was dissolved in methanol-THF (2:1, 1.5 mL). To this was added 1 M LiOH (aq) (155 µl) and the mixture was stirred at 60 °C for 3-5 hrs. Glacial acetic acid (50 µl) was added and the mixture was concentrated, dissolved in methanol and purified by reversed phase HPLC.

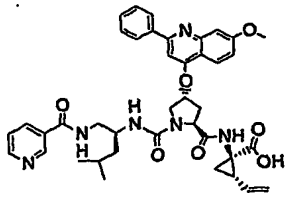
Example 167



(1R, 2S)-1-{[(2S, 4R)-1-{(1S)-1-[(3-Fluoro-benzoylamino)-methyl]-3-methylbutylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (167)

General procedure 1A was followed using 3-fluorobenzoyl chloride (12 mg) as acyl chloride which gave the title compound as a solid (13.6 mg, 50 %). M+H$^+$738.1.

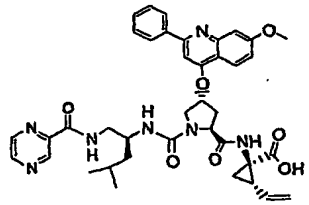
Example 168



(1R, 2S)-1-{[(2S, 4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-1-((1S)-3-methyl-1-{[(pyridine-3-carbonyl)-amino]-methyl}-butylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (168)

General procedure 1A was followed using nicotinoyl chloride (10.5 mg) as acyl chloride which gave the title compound as a solid (10 mg, 37 %). M+H$^+$721.1.

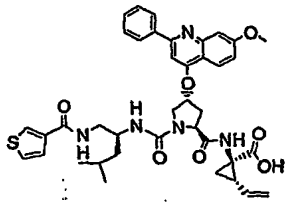
Example 169



(1R, 2S)-1-{[(2S, 4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-1-((1S)-3-methyl-1-{[(pyrazine-2-carbonyl)-amino]-methyl}-butylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (169)

General procedure 1B was followed using pyrazine-2-carboxylic acid (5 mg) as acid which gave the title compound as a solid (5.7 mg, 25 %). M+H$^+$722.1.

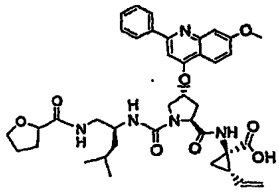
Example 170



(1R, 2S)-1-{[(2S, 4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-1-((1S)-3-methyl-1-{[(thiophene-3-carbonyl)-amino]-methyl}-butylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (170)

General procedure 1A was followed using thiophene-3-carbonyl chloride (11 mg) which gave the title compound as a solid (4.3 mg, 16 %). M+H$^+$726.1.

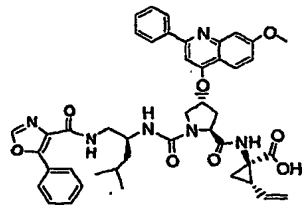
Example 171



(1R, 2S)-1-{[(2S, 4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-1-((1S)-3-methyl-1-{[(tetrahydro-furan-2-carbonyl)-amino]-methyl}-butylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (171)

General procedure 1B was followed using tetrahydrofurane-2-carboxylic acid (4.5 mg) as acid which gave the title compound as a solid (7.9 mg, 36 %). M+H$^+$714.1.

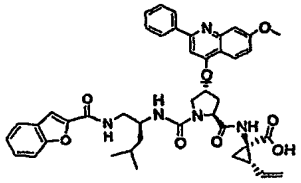
Example 172



(1R, 2S)-1-{[(2S, 4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-1-((1S)-3-methyl-1-{[(5-phenyl-oxazole-4-carbonyl)-amino]-methyl}-butylcarbamoyl)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (172)

General procedure 1B was followed using 5-phenyl-oxazole-4-carboxylic acid (7.5 mg) as acid which gave the title compound as a solid (7.5 mg, 31 %). M+H$^+$787.1.

Example 173



(1R, 2S)-1-{[(2S, 4R)-1-((1S)-1-{[(Benzofuran-2-carbonyl)-amino]-methyl}-3-methyl-butylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (173)

General procedure 1B was followed using benzofuran-2-carboxylic acid (6.5 mg) as acid which gave the title compound as a solid (5.4 mg, 23 %). M+H$^+$760.1.

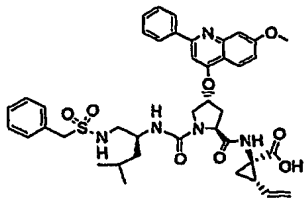
General procedure 2 for the preparation of compounds 174-176

To a solution of the sulphonyl chloride (0.075 mmol) in DCM (0.5 mL) was added $NaHCO_3$ (s) (60 mg) and a solution of the amine 166 (25 mg, 0.037 mmol) in THF (1 mL). The resulting mixture was stirred at room temperature for 18 hrs, filtered and then shaken with PS-trisamine (tris-(2-aminoethyl)aminomethyl polystyrene, 3.91 mmol/ g, ~50 mg) for 5 hrs.

The mixture was filtered and the polymer was washed successively with DCM, THF and methanol. The solid residue resulting from evaporation of the combined filtrates was dissolved in MeOH-THF (2:1, 1.5 mL) and treated with 1 M LiOH (aq) (170 $\mu$l) at 50 °C for reaction times varying from 18 hrs to one week depending on the actual

structure. The reaction was monitored by HPLC-MS. The mixture was acidified with acetic acid and evaporated to dryness. The residue was dissolved in methanol and purified by reversed phase HPLC.

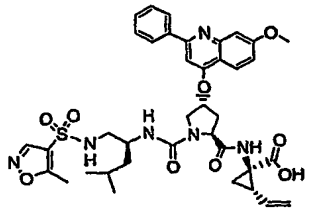
Example 174



(1R, 2S)-1-({(2S, 4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-1-[(1S)-3-methyl-1-(phenylmethanesulphonylamino-methyl)-butylcarbamoyl]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (174)

General procedure 2 was followed using $\alpha$-toluenesulphonyl chloride (14 mg) as sulphonyl chloride which gave the title compound as a white solid (4.9 mg, 17 %). $M+H^+$770.1.

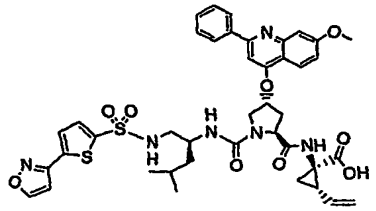
Example 175



(1R, 2S)-1-[((2S, 4R)-4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-1-{(1S)-3-methyl-1-[(5-methyl-isoxazole-4-sulphonylamino)-methyl]-butylcarbamoyl}-pyrrolidine-2-carbonyl)-amino]-2-vinyl-cyclopropanecarboxylic acid (175)

General procedure 2 was followed using 5-methyl-isoxazole-4-sulphonyl chloride (14 mg) as sulphonyl chloride which gave the title compound as a white solid (1.6 mg, 6 %). M+H$^+$761.0.

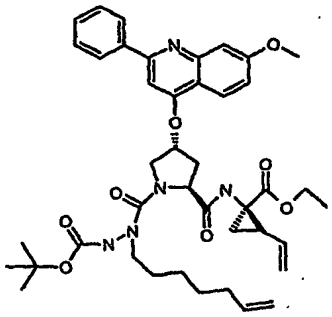
Example 176



(1R, 2S)-1-{[(2S, 4R)-1-{(1S)-1-[(5-Isoxazol-3-yl-thiophene-2-sulphonylamino)-methyl]-3-methyl-butylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (176)

General procedure 2 was followed using 5-isoxazol-3-yl-thiophene-2-sulphonyl chloride (19 mg) as sulphonyl chloride which gave the title compound as a white solid (3.0 mg, 10 %). M+H$^+$828.98.

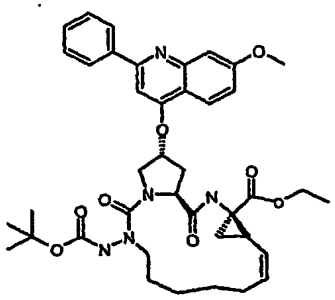
Example 177



1-{[1-(N'-tert.Butoxycarbonyl-N-hept-6-enyl-hydrazinocarbonyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (177)

Compound 62 (200 mg, 0.4 mmol) was dissolved in tetrahydrofuran (10 mL). A tea-spoon of sodium hydrogencarbonate was added, followed by phosgene (1.8 µl, 1.9 M in toluene). The reaction mixture was stirred for 30 min and filtrated. The solvent was evaporated and the crude chloride was re-dissolved in dichloromethane (10 mL). Sodium hydrogencarbonate (1 tea-spoon) and *N'*-hept-6-enyl-hydrazinecarboxylic acid *tert.*butyl ester (182 mg, 0.8 mmol). The reaction mixture was stirred at room temp. for 40 h. and then filtrated and purified by silica chromatography (1 % methanol in ether → 2 % methanol in ether) to give pure 177 (240 mg, 79 %).

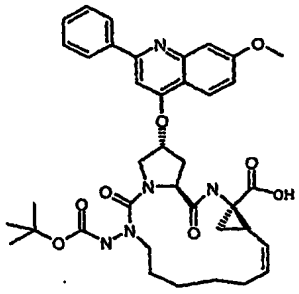
Example 178



14-tert.Butoxycarbonylamino-18-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,15-dioxo-3,14,16-triaza-tricyclo[14.3.0.0*4,6*]nonadec-7-ene-4-carboxylic acid ethyl ester (178)

Compound 177 (200mg, 0.26 mmol) was dissolved in degassed dichloromethane (30 mL). Hoveyda – Grubbs catalyst II generation (16 mg, 0.026 mmol) was then added and the mixture was refluxed under argon atmosphere overnight. The solvent was then evaporated and the crude product was purified by silica chromatography (1 % methanol in ether) which gave 39 mg (20 %) of the title product. MS ($M+H^+$) 728.2

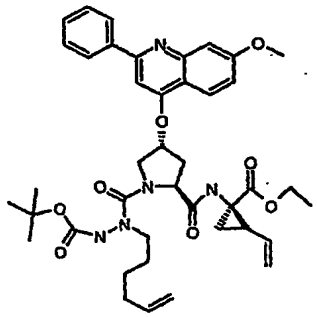
Example 179



14-tert.Butoxycarbonylamino-18-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,15-dioxo-3,14,16-triaza-tricyclo[14.3.0.0*4,6*]nonadec-7-ene-4-carboxylic acid (179)

Compound 178 (39 mg, 0.054 mmol) was dissolved in tetrahydrofuran (3.5 mL), water (1.75 mL) and methanol (1.75 mL). Lithium hydroxide (430 µl, 1 M in water) was then added and the reaction was stirred at room temperature for 24 h. The volume was reduced to half and water (10 mL) was added. Acidification (pH=5) followed by extraction with chloroform gave 34 mg (90 %) of the pure acid 179. MS ($M+H^+$) 700.2

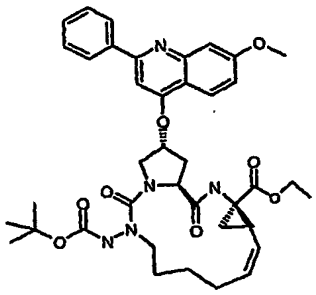
Example 180



1-{[1-(N'-tert.Butoxycarbonyl-N-hex-5-enyl-hydrazinocarbonyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cycloprpanecarboxylic acid ethyl ester (180)

The title compound was prepared from compound 62 (800 mg, 1.6 mmol) and *N'*-hex-5-enyl-hydrazinecarboxylic acid tert.butyl ester (620 mg, 2.9 mmol) by the same procedure as described in Example 177 which gave 1 g (85 %). MS ($M+H^+$) 742.37

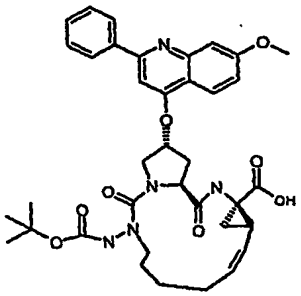
Example 181



13-tert.Butoxycarbonylamino-17-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13,15-triaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carboxylic acid ethyl ester (181)

The title compound was prepared from 180 (400 mg, 0.54 mmol) following the same procedure as described for compound 178. The crude product was purified by silica chromatography (1 % methanol in ether) to give 67 mg (17 %) of pure 181. MS ($M+H^+$) 714.29

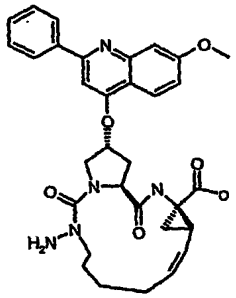
Example 182



13-tert.Butoxycarbonylamino-17-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13,15-triaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carboxylic acid (182)

The title compound was prepared from MA394-45 (67 mg, 0.09 mmol) by the same procedure as described for 179 which gave 46 mg (71 %) of the pure acid 182. Chloroform was replaced by 1, 2-dichloroethane for this compound. MS ($M+H^+$) 686.33

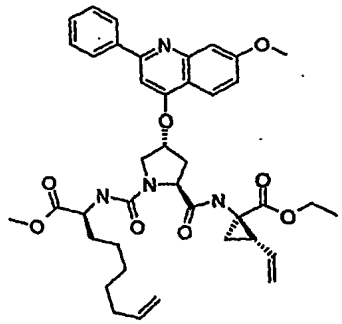
Example 183



13-tert.Amino-17-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13,15-triaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carboxylic acid (183)

Compound 182 (10 mg) was dissolved in dichloromethane (4 mL). Trifluoromethanesulphonic acid (4 mL) was added and the mixture was left at 50° C for 6 hours. The solvent was removed and the residue was washed with acetonitrile which gave 3 mg of the pure title product (35 %). MS ($M+H^+$) 586.25

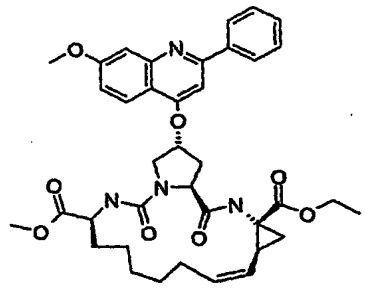
Example 184



1-{[1-(1-Methoxycarbonyl-oct-7-enylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (184)

The title compound was prepared from compound 62 (380 mg, 0.758 mmol) and 2-aminononan-8-enyl-carboxylic acid methyl ester (250 mg, 1.89 mmol) using the conditions described in Example 177 which gave the pure product (405 mg, 75 %).

Example 185

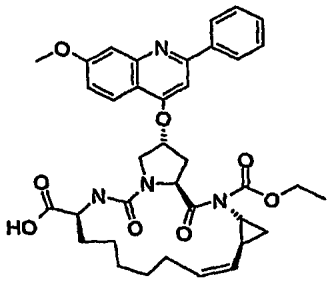


19-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-2,16-dioxo-3,15,17-triaza-tricyclo[15.3.0.0*4,6*]icos-7-ene-4,14-dicarboxylic acid 4-ethyl ester 14 methyl ester (185)

Compound 184 (170mg, 0.2385 mmol) was dissolved in dichloromethane (40 mL) and degassed by bubbling nitrogen for 20 min. Hoveyda – Grubbs catalyst II generation (10 mg, 0.016 mmol, 6.7 mol %) was then added and the mixture was

refluxed under nitrogen atmosphere overnight. The solvent was then evaporated, catalyst and salts were removed by flash chromatography (5% methanol in chloroform) and the crude product (120 mg, 73% yield, 85-90% purity) was used in next step MS ($M+H^+$) 685

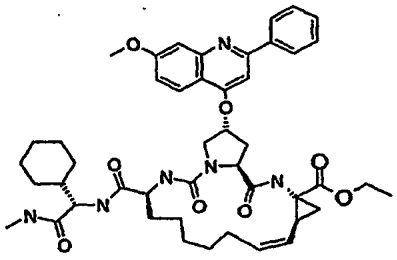
Example 186



19-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-2,16-dioxo-3,15,17-triaza-tricyclo[15.3.0.0*4,6*]icos-7-ene-3,14-dicarboxylic acid 3-ethyl ester(186)

Compound 185 (120 mg, 0.175 mmol) was dissolved in dioxane (9 mL) and water (6 mL). Lithium hydroxide (12 mg, 0.526 mmol) was added and the reaction was stirred at room temperature for 3.5 h. The mixture was acidified with acetic acid to pH=5, and co-evaporated with toluene. The crude product was used in the next step. MS ($M+H^+$) 671

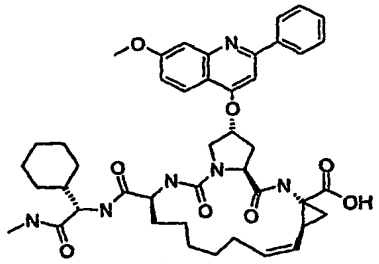
Example 187



14-[(Cyclohexyl-methylcarbamoyl-methyl)-19-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,16-dioxo-3,15,17-triaza-tricyclo[15.3.0.0*4,6*]icos-7-ene-4-carboxylic acid 3-ethyl ester (187)

Compound 186 (crude, 100 mg), indanolamine (33 mg, 0.209 mmol) and Hunig's base (DIEA) (0.2 mL) were dissolved in DMF (14 mL). After stirring at 0 °C for 10 min HATU was added. The reaction was monitored by LC-MS. After 5h conversion was 100%. DMF and DIEA were removed *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried and concentrated *in vacuo*. The crude yield was 120 mg, the purification by prep. HPLC gave 21 mg (25%) of title product. MS ($M+H^+$) 802

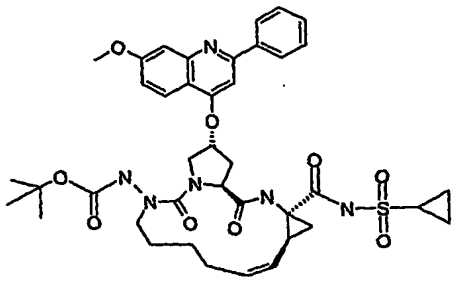
Example 188



14-[(Cyclohexyl-methylcarbamoyl-methyl)-19-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,16-dioxo-3,15,17-triaza-tricyclo[15.3.0.0*4,6*]icos-7-ene-4-carboxylic acid (188)

To a solution of the ester 187 (19 mg, 0.024 mmol) in the mixture of THF (0.2 mL) and methanol (0.3 mL) was added solution of LiOH (6 mg, 0.237 mmol) in 0.15 ml of water. The resulting mixture was stirred at 60 °C for 3.5h. After cooling to room temperature, acetic acid was added (30 eq). The mixture was co-evaporated with toluene. The residue was distributed between chloroform and water phases, the water one was extracted with chloroform and ethyl acetate, organic phases were combined, dried over sodium sulphate, evaporated to give 15 mg of pure product. MS ($M+H^+$) 774

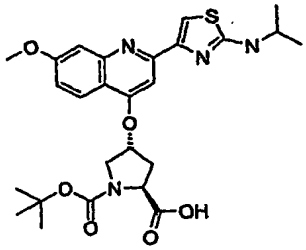
Example 189



[14- Cyclopropanesulfonylaminocarbonyl-17-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13,15-triaza-tricyclo[13.3.0.0*4,6*]octadec-7-en-13-yl]-carbamic acid ter.butyl ester (189)

To the acid 182 (19 mg, 0.028 mmol) in 0.5 ml of DMF was added 5.5 mg (0.044 mmol) of DMAP and 10.7 mg (0.056 mmol) of EDC. After 6.5h of stirring 20 mg of cyclopropylsulphone amide and 0.04 ml of DBU were added. The mixture was stirred overnight, acidified with 5% citric acid (in water) and extracted with ethyl acetate. Dried, evaporated, purified by 5% to 10% methanol in chloroform (or prep LC-MS) which gave 8 mg of the title compound (37%)
MS ($M+H^+$) 783

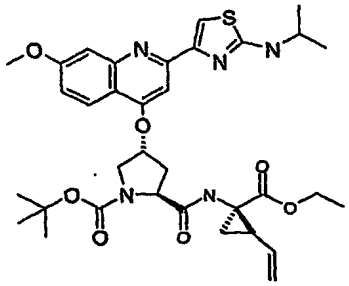
Example 190



4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1,2-dicarboxylic acid 1-tert.butyl ester (190)

To a stirred solution of N-Boc-trans-4-hydroxy-L-proline (221 mg, 0.96 mmol) in DMSO was added potassium tert.butoxide (320 mg, 2,9 mmol). After 1h 2-[2-isoprpylamino)-1,3-thiazol-4-yl]-7-methoxyquinolin-4-ol (319 mg, 0,96 mmol) was added and the mixture was stirred at 70 °C for 72 hours. The mixture was diluted with water and extracted with ethyl acetate. The product was used without further purification. Yield 429 mg, 85%.

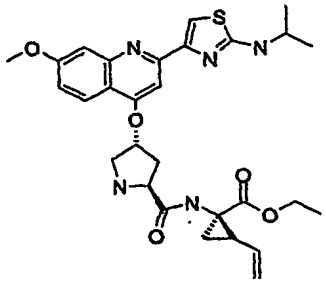
Example 191



2-(1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-1-carboxylic acid tert.butyl ester (190)

Compound 190 (300 mg, 0.56 mmol) was reacted with 1-amino-2-vinyl-cyclopropanecarboxylic acid ethyl ester (130 mg, 0.84 mmol) as described in Example 61 which gave the title compound (302 mg, 80 %).

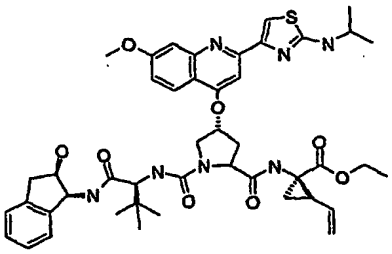
Example 192



1-({4-[2-(2-Isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl}-amino)- 2-vinyl-cyclopropanecarboxylic acid ethyl ester (192)

Compound 191 (302 mg, 0.45 mmol) was treated as described in Example 62 which gave the title compound (195 mg, 76%).

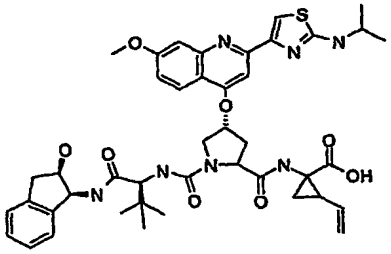
Example 193



1-({1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl}-amino-2-vinyl-cycloprpoanecarboxylic acid ethyl ester (193)

Compound 192 (80 mg, 0.14 mmol) was treated as described in Example 63 which gave the title product (87 mg, 72%).

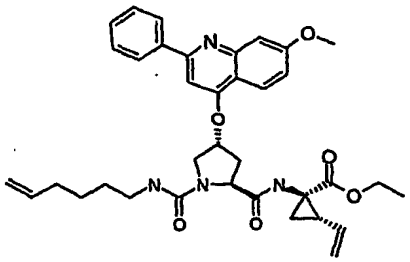
Example 194



1-({1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-pyrrolidine-2-carbonyl}-amino-2-vinyl-cycloprpoanecarboxylic acid (194)

The ethyl ester of compound 193 (80 mg, 0.09 mmol) was hydrolyzed following the procedure described in Example 64 which gave the title product Yield after preparative LC-MS (7.5 mg, 10%).

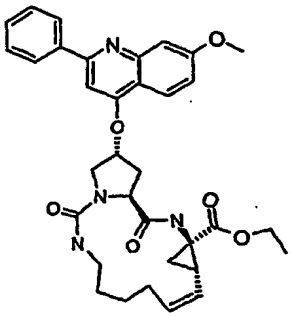
Example 195



1-{[1-Ethylcarbamoyl-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (195)

Reaction of compound 62 (330 mg, 0.66 mmol), phosgene (1.6 ml, 1.9 M in toluene, 3 mmol) and hex-5-enylamine hydrochloride (500 mg, 3.68 mmol) following the procedure described in Example 177 gave the pure title product (328 mg, 80 %), MS ($M+H^+$) 627.

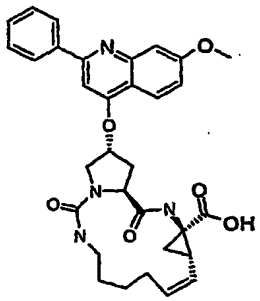
Example 196



17-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13,15-triaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carboxylic acid ethyl ester (196)

Compound 195 (200 mg, mol) was dissolved in degassed dry dichloromethane (200 mL), bubbled with nitrogen. Then Hoveyda-Grubbs (second generation) catalyst (5 mg, 2 mol %) was added and the reaction mixture was refluxed for 20 h under nitrogen. The resulting mixture was cooled down to room temperature and concentrated by rotary evaporation. The resulting oil was purified by column chromatography on YMC silica (ethyl acetate – toluene 1:1 to 9:1) to give 55 mg of the title compound as a beige solid. Yield 29%. MS ($M+H^+$) 599.

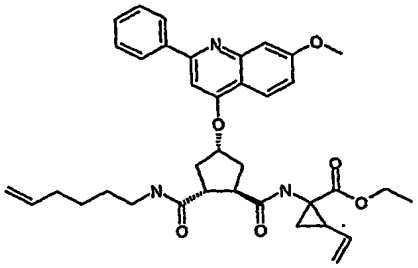
Example 197



17-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13,15-triaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carboxylic acid (197)

Compound 196 (55 mg, mol) was dissolved in 2 ml of methanol and mixed with 3 eq. of aqueous NaOH and heated for 2 h at 60 °C in a closed vial. The reaction mixture was then extracted into ethyl acetate. The water solution was collected and acidified with 1N HCl solution to pH 2. The resulting solution was concentrated by rotary evaporation, dissolved in methanol and purified by preparative HPLC (acetonitrile-water) to give 34 mg of the title product. Yield 65%. MS ($M+H^+$) 571.

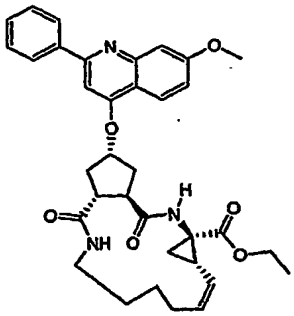
Example 198



1-{[2-Hex-5-enylcarbamoyl-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cycloprpanecarboxylic acid ethyl ester (198)

The tert.butyl ester of compound 35 was removed according to the procedure described in Example 39. The afforded acid (724 mg, 1.33 mmol), hex-5-enylamine hydrochloride (271 mg, 2 mmol) and diisopropylethylamine (1.85 ml, 10.65 mmol) was dissolved in DMF (20 mL) and cooled to 0°C. After 30 min. HATU (608 mg, 1.6 mmol) was added and the flask was removed from the ice-bath. The reaction was followed with LC-MS. After 3 h the reaction mixture was extracted between EtOAc (100 mL) and aqueous sodium hydrogencarbonate (15 mL). The EtOAc-phase was dried over magnesium sulphate, evaporated and purified by chromatography on silica gel (25% EtOAc in hexane → 50 % EtOAc in hexane) to give the pure title product (726 mg, 87%). MS ($M+H^+$): 525.8

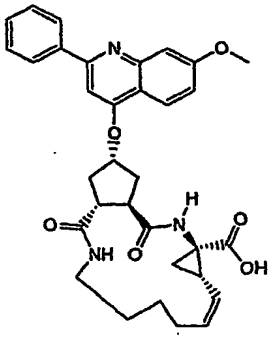
Example 199



17-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13-diaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carboxylic acid ethyl ester (199)

Compound 198 (363 mg, 0.58 mmol) was dissolved in degassed dichloromethane (100 mL). Hoveyda-Grubbs catalyst 2:nd generation (26 mg, 0.041 mmol) was added and the mixture was refluxed under argon atmosphere overnight. The reaction mixture was evaporated on silica and purified by silica gel chromatography (50 % EtOAc in hexane → 70 % EtOAc in hexane) to give the pure title product (111 mg, 32%). MS ($M+H^+$): 597.7

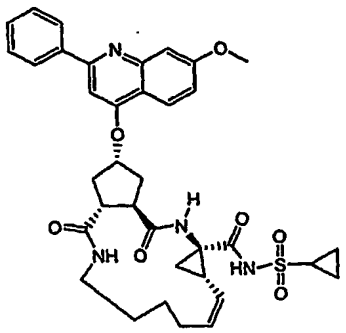
Example 200



17-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13-diaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carboxylic acid (200)

Compound 199 (95 mg, 0.159 mmol) was dissolved in tetrahydrofuran (10 mL), methanol (5 mL) and water (4 mL) Lithium hydroxide (40 mg, 1.67 mmol) was dissolved in water (1 mL) and added. The reaction mixture was heated to 65°C. After 3 h the reaction mixture was cooled, acidified with aqueous HCl (pH=5), evaporated on silica and purified by silica gel chromatography (10 % MeOH in dichloromethane → 15 % MeOH in dichloromethane) to give the pure title product (65 mg, 72 %). MS ($M+H^+$): 569.8

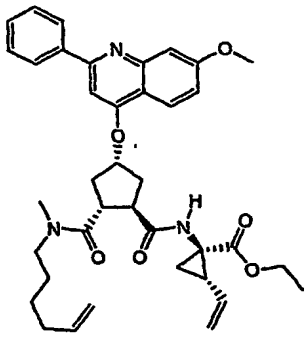
Example 201



Cyclopropanesulphonic acid [17-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13-diaza-tricyclo[13.3.0.0*4,6*octadec-7-ene-4-carbonyl]-amide (201)

Compound 200 (65 mg, 0.12 mmol), DMAP (21 mg, 0.17 mmol) and EDAC (44 mg, 0.23 mmol) was dissolved in DMF (0.2 mL). The reaction mixture was stirred for 5 h at R.T. whereafter cyclopropylsulfonamide (69 mg, 0.57 mmol) and DBU (80 µl, 0.57 mmol) was added. After stirring at R.T overnight the reaction mixture was extracted between EtOAc (80 mL) and aqueous citric acid (10 %, 2 x 15 mL). The organic phase was dried over $MgSO_4$, evaporated on silica and purified twice by chromatography on silica gel (5 % MeOH in dichloromethane → 15 % MeOH in dichloromethane) which gave a syrup. This syrup was dissolved in a small volume acetonitrile and precipitated with ethyl ether to give the pure title product (19 mg, 23 %). MS (M +$H^+$): 673.2

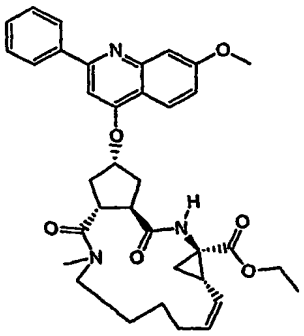
Example 202



1-{[2-Hex-5-enyl-methyl-carbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino-2-vinyl-cyclopropanecarboxylic acid ethyl ester (202)

The tert.butyl ester of compound 35 was removed according to the procedure described in Example 39. The afforded acid (850 mg, 1.56 mmol), N -methyl hex-5-enylamine hydrochloride (380 mg, 2,5 mmol) and diisopropylethylamine (2,3 ml, 13,4 mmol) was dissolved in DMF (60 mL) and cooled to 0°C. After 30 min. HATU (0,76 mg, 2,0 mmol) was added and the flask was removed from the ice-bath. The reaction was followed with TLC. After 2 h the reaction mixture was added to 5% citric acid and extracted three times with ethyl acetate. The organic phase was dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by silica gel chromatography which gave the title product (820 mg, 82%.

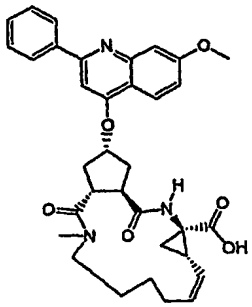
Example 203



17-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carboxylic acid ethyl ester (203)

Compound 202 (648 mg, 1,01 mmol) was dissolved in degassed dichloroethane (500 mL). Hoveyda-Grubbs catalyst 2:nd generation (35 mg, 0.055 mmol) was added and the mixture was refluxed under argon atmosphere overnight. The reaction mixture was evaporated on silica and purified by chromatography on silica gel (30 % EtOAc in toluene → 50 % EtOAc in toluene) to give the pure title product (230 mg mg, 37%). MS (M +$H^+$): 612.8

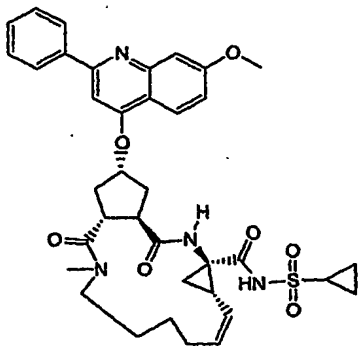
Example 204



17-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carboxylic acid ethyl ester (204)

Compound 203 (260 mg, 0.42 mmol) was dissolved in 1,4-dioxan (20 mL), 1.0 M Lithium hydroxide (6,0 ml ) was added and the mixture was stirred at room temperature overnight and then for six hours at 60°C. The mixture was added to 5% citric acid and extracted 3 times with ethyl acetate. The organic phase was dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by silica gel chromatography with DCM and 5% MeOH which gave the title product (130mg, 53%). MS (M + H) : 584,7

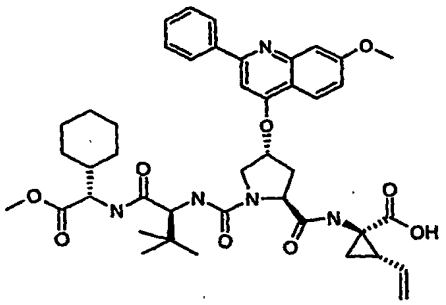
Example 205



Cyclopropanesulphonic acid [17-(7-methoxy-2-phenyl-quinolin-4-yloxy)-13-methyl-2,14-dioxo-3,13-diaza-tricyclo[13.3.0.0*4,6*octadec-7-ene-4-carbonyl]-amide (205)

Compound 204 (58,3 mg, 0.1 mmol), DMAP (18,3 mg, 0.15 mmol) and EDAC (38,7 mg, 0.2 mmol) was dissolved in DMF (1,0 mL). The reaction mixture was stirred overnight at R.T. whereafter cyclopropylsulphonamide (60,5 mg, 0.5 mmol) and DBU (76 $\mu$g, 0.5 mmol) was added. After stirring at R.T overnight the reaction mixture was added to 5% citric acid and extracted three times with ethyl acetate. The organic phase was dried over sodium sulphate and evaporated .The afforded residue was purified two times by silica gel chromatography which gave the title product (20 mg). MS (M + H ) 687,8.

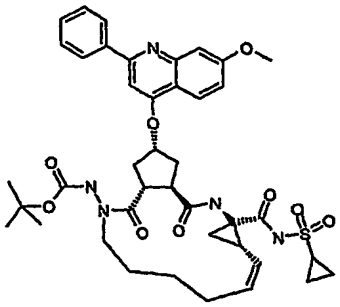
Example 206



1-{[1-{1-[(Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (206).

Compound 160 was dissolved in dichloromethane (3mL) and solid sodium bicarbonate (100 mg) and phosgene 20% in toluene (0.1 mL) was added. After 30 min at room temperature the mixture was concentrated to dryness. (S)-(2S-2-Amino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (12 mg in dichloromethane 2 mL) was added. After 3days of agitation at room temperature, the reaction mixture was filtered, concentrated to dryness and purified on preparative HPLC-MS which gave the title product (4.4 mg). $M+H^+$ 784.7.

Example 207



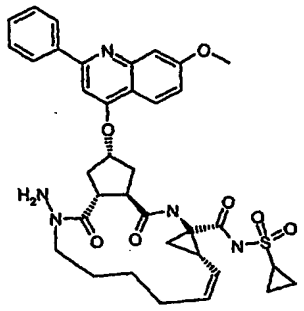
[4-Cyclopropanesulphonylaminocarbonyl-17-(7-methoxy-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13-diaza-tricyclo[13.3.0.0*4,6*]octadec-7-en-13-yl]-carbamic acid tert.butyl ester (207)

N'-Hex-5-en-(E)-ylidene-hydrazinecarboxylic acid tert.butyl ester was prepared according to the procedure described in Example 46 and 47 but starting from hex-5-en-ol instead of hept-6-en-ol.

Compound 35 was then treated as described in Example 48 but using the above described N'-Hex-5-en-(E)-ylidene-hydrazinecarboxylic acid tert.butyl ester instead of the corresponding hept-6-en derivative followed by macrocyclisation as described in Example 49 and hydrolysis of the ethyl ester as described in Example 50 gave the acid.

The afforded acid (58 mg, 0.0846 mmol) was dissolved in dry DMF (7 mL) and DIEA was added drop wise during one minute. The solution was stirred at room temperature for 1h prior to the addition of a solution containing cyclopropylsulfonamide (41 mg, 0.338 mmol), DMAP (41.3mg, 0.338 mmol) and DBU (50 $\mu$L, 0.338 mmol) in dry DMF (1.5 mL). The solution was stirred at room temperature for 5 days. The solution was diluted with EtOAc (50 mL) and washed with sat. $NaHCO_3$. The aqueous phase was extracted with DCM. The combined organic layers were dried, concentrated and subjected to purification by HPLC, which gave the title compound as a white solid (14.3 mg, 0.018 mmol), Purity by HPLC > 95%, $M+H^+$ 788.3.

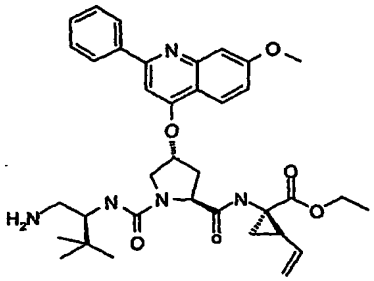
Example 208



Cyclopropanesulphonic acid[13-amino-17-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,14-dioxo-3,13-diaza-tricyclo[13.3.0.0*4,6*]octadec-7-ene-4-carbonyl]-amide trifluoroacetic acid salt (208)

Compound 207 (2.4 mg, 0.00304mmol) was kept in TFA-DCM 1:2 (3mL) at room temperature for 60 min. Toluene (3 mL) was added. The sample was co-evaporated to dryness to afford the title compound (2.1 mg, 0.0026 mmol) Purity by HPLC >95%. $M+H^+$ 688.3.

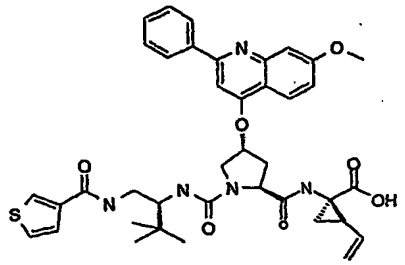
Example 209



1-{[1-(1-Aminomethyl-2,2-dimethyl-propylcarbamoyl-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (209)

The title compound was prepared from compound 62 (1.22 g, 2.43 mmol) by following the procedure described for the preparation for compound 165 but using methanesulphonic acid 2-tert.butoxycarbonylamino-3,3-dimehtyl-butyl ester instead of methanesulphonic acid 2-tert.butoxycarbonylamino-4-mehtyl-pentyl ester, in Example 165 step i). Reduction of the azide as described in Example 166 gave the title compound (1.49 g, 95 %). Purity according to HPLC > 95%, $M+H^+$ 644.2.

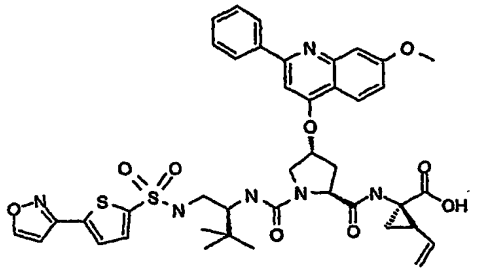
Example 210



1-{[1-(2,2-Dimethyl-1-{[thiophene-3-carbonyl)-amino]-methyl}-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (210)

Compound 209 (100 mg, 0,155 mmol) was reacted according to the general procedure 1A for the preparation of compounds 167-173, using thiophene-3-carbonyl chloride (28.5 mg, 0.194 mmol) as acyl chloride which gave the title compound as a white solid (45 mg, 40%). Purity according to HPLC > 95%, $M+H^+$ 726.

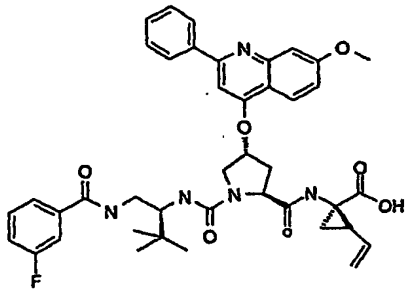
Example 211



1-{[1-{1-[(5-Isoxazol-3-yl-thiophene-2-sulphonylamino)-methyl]- 2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (211)

Compound 209 (25 mg, 0.039 mmol) was reacted according to the general procedure 1A for the preparation of compounds 167-173, using 5-isoxazole-3-yl-thiophene-2-sulphonyl chloride (14.5 mg, 0.058 mmol) as acyl chloride which gave the title compound as a white solid (1.8 mg, 6%). Purity according to HPLC was > 94%, $M+H^+$ 829.

Example 212

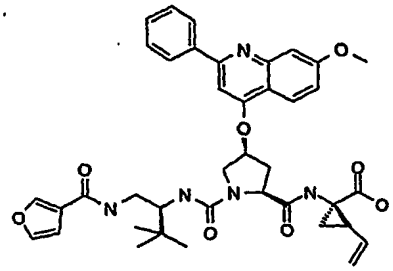


1-{[1-(3-Fluoro-benzoylamino)-methyl]-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (212)

Compound 209 (25 mg, 0.039 mmol) was reacted according to the general procedure 1A for the preparation of compounds 167-173, using 3-fluorobenzoyl

chloride (12.3 mg, 0.078 mmol) as acyl chloride which gave the title compound as a white solid (4.1 mg, 14%). Purity according to HPLC was > 94%, $M+H^+$ 738.

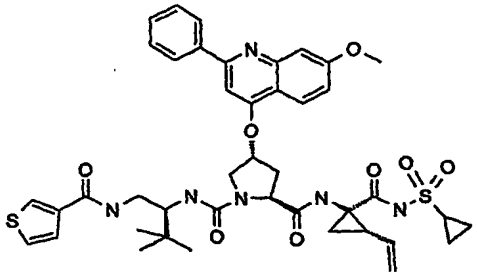
Example 213



1-{[1-(1{[(-Furan-3bcarbonyl)- amino]-methyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (213)

Compound 209 (25 mg, 0.039 mmol) was reacted according to the general procedure 1B for the preparation of compounds 167-173, using 3-furanoic acid (5.5 mg, 0.049 mmol) as acyl chloride which gave the title compound as a white solid (4.1 mg, 14%). Purity according to HPLC was > 99%, $M+H^+$ 710.

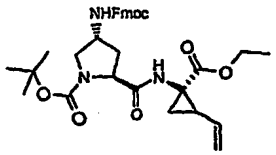
Example 214



4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-1,2-dicarboxylic acid 2-[(1-cyclopropanesulphonylaminocarbonyl-2-vinyl-cyclopropyl)-amide] 1-[(2,2-dimethyl-1-{[(thiophene-3-carbonyl)amino]-methyl}-propyl)-amide (214)

To solution of compound 210 (42.2mg, 0.058mmol) in chloroform (3 ml) was added cyclopropylsulphonamide (14 mg, 0.116 mmol) followed by diisopropylethylamine (60.5 $\mu$l, 0.17 mmol). The solution was stirred at RT for 10 min and then at -20°C for 30 min. PyBOP (121 mg, 0.116 mmol) was then added as a solid. The solution was kept at -20°C for 10 days. The solution was then poured into aqueous $NaHCO_3$ (sat.) and washed with water. The organic layer was dried, concentrated and subjected to purification by HPLC, affording the title compound as a white solid (2.3 mg, 0.0028 mmol), Purity by HPLC>95%, $M+H^+$ 830.

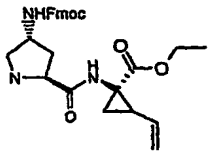
Example 215




4-Amino-2-(1-ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-pyrrolidine-1-carbocyclic acid tert.butyl ester (215)

(2S,4R) Fmoc-4-amino-1-Boc-pyrrolidine-2-carboxylic acid (5.3 g, 11.8 mmol) was dissolved in DCM (100 mL), HATU (4.94 g, 12.99 mmol), DIEA (4.63 ml, 26.57 mmol) and vinylcyclopropylglycine ethyl ester (2.26 g, 11.81 mmol) were added successively. The mixture was stirred for 16 h at room temperature, and was then diluted with DCM (50 mL), washed with citric acid (10% aq), water, $NaHCO_3$ (sat.aq) and water. The organic phase was dried over $Na_2SO_4$ and concentrated to afford a beige solid foam (8.11 g) which was subjected to silica gel column chromatography to afford the title compound (7.14 g, 12.11 mmol).

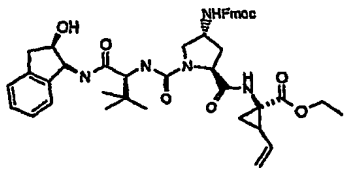
Example 216



1-[(4-Amino-pyrrolidine-2-carbonyl)-amino]-2-vinyl-cyclopropanecarboxylic acid ethyl ester (216)

Compound 215 (3.65 g, 6.04 mmol) was treated with a solution of TFA/DCM (10ml TFA, 50ml DCM) for 2.5h and then concentrated to afford the titled compound (2.99 g, 6.12 mmol).

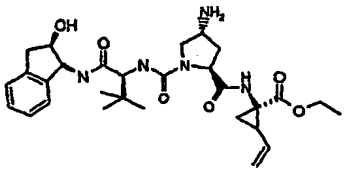
Example 217




1-({4-Amino-1-[1-(2-hydroxy-indan-1-ylcarbamoyl-2,2-dimethyl-propylcarbamoyl]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid ethyl ester (217)

The aminoproline derivative 216 (2.96 g, 6.04 mmol) was stirred together with phosgene (1.93 M in toluene, 4 ml, 7.55 mmol) for 10 min. The solvents and excess of phosgene were evaporated. The residue was dissolved in DCM (30 mL) and t-Bug-aminoindanol (1.9 g, 7.24 mmol) was added as a solution in DCM (30 mL), followed by $NaHCO_3$ (2 g). The mixture was stirred for 48h, then diluted with DCM, washed with water, 10% citric acid and $NaHCO_3$ (sat, aq), dried over $Na_2SO_4$, and evaporated to dryness. The residue was subjected to column chromatography purification, EtOAc-hexane 0-30% to afford the title compound (1 g, 1.3 mmol).

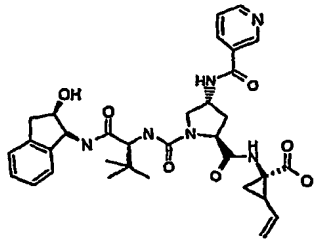
Example 218



1-({4-Amino-1-[1-(2-hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cycloprpanecarboxylic acid ethyl ester (218)

Compound 217 (595 mg, 0.765 mmol) was dissolve din DMF (20 mL) and treated with Si-piperazine (0.08 mmol/g, 4.78 g, 3.82 mmol) for 48h. The silica was filtered and washed once with DMF and then with several portions of DCM. The solvents were evaporated and the residue subjected to column chromatography to afford the title compound (170 mg, 0.3 mmol).

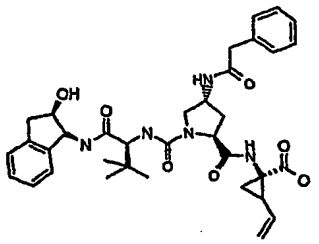
Example 219



1-({1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-[(pyridine-3-carbonyl)-amino]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (219)

To a stirred solution of compound 218 (35 mg, 0.064 mmol) in DCM (1 mL), was added DIEA (0.12 mmol, 19 $\mu$L) and nicotinoyl chloride hydrochloride (0.12 mmol, 17 mg).The solution was stirred at RT for 18h, PS-trisamine was added then stirred at RT for 4h. After filtration, the solution was washed with citric acid (10% aq) and $NaHCO_3$ (sat, aq), the organic phase was dried over $Na_2SO_4$ and concentrated. The residue was dissolved in THF:MeOH (2:1, 1.5 mL). LiOH (1N aq, 3.2 mmol, 320 $\mu$L) was added. The solution was stirred at 60 °C for 24h. Acetic acid was added and then concentrated. The residue was dissolved in MeOH and subjected to purification by HPLC, affording the title compound (19.5 mg, 0.03 mmol). Purity by HPLC>98%, $M+H^+$ 633.1.

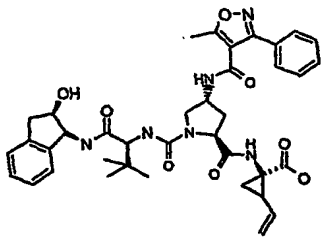
Example 220



1-({1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-phenylacetamino-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (220)

The procedure described in Example 219 but using phenyl acetyl chloride instead of nicotinoyl chloride hydrochloride, was followed which gave the title compound (12.7 mg, 0.019 mmol). Purity by HPLC>90%, $M+H^+$ 646.1.

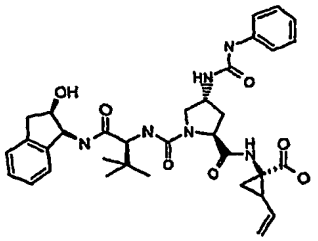
Example 221



1-({1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-[(5-methyl-3-phenyl-isoxazole-4-carbonyl)-amino]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (221)

The procedure described in Example 219 but using 5-methyl-3-phenyl-isoxazole-4-carbonyl chloride instead of nicotinoyl chloride hydrochloride, was followed which gave the title compound (3.6 mg, 00055 mmol). Purity by HPLC>98%, $M+H^+$ 713.1.

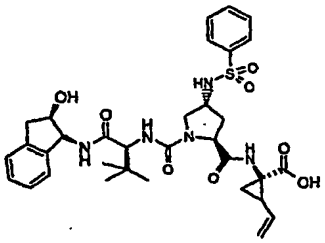
Example 222



1-{[1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(3-phenyl-ureido)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (222)

To a stirred solution of compound 218 (30 mg, 0.054 mmol) in acetonitrile:dichloromethane (2:1, 3 mL), triethylamine (0.0648 mmol, 9 $\mu$L) and phenylisocyanate (0.0648 mmol, 7 $\mu$L) was added .The solution was stirred at room temperature for 3h, methanol was added (1 mL) and then it was concentrated. The residue was dissolved in methanol and subjected to purification by HPLC, affording the ester compound as a white solid (32.7mg, 0.047 mmol), Purity by HPLC>95%, $M+H^+$ 675.31. LiOH 1N aq. (0.47mmol, 475 $\mu$L) was added to the ester dissolved in THF:MeOH (2:1). The reaction was stirred at 50 °C for 15 min and then at 8 °C for 12 h followed by addition of acetic acid (0.98 mmol, 53 $\mu$L) before concentration. The residue was dissolved in MeOH and subjected to purification by HPLC, affording the title compound as a white solid (3.8 mg, 0.006 mmol), Purity by HPLC>98%, $M+H^+$ 675.31.

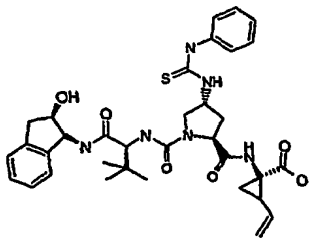
Example 223



1-({4-Benzenesulphonylamino-1-[1-(2-hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (223)

To a stirred solution of compound 218 (30 mg, 0.054 mmol) in DCM (2 mL), DIEA (0.0648 mmol, 11.5 $\mu$L) and phenysulfonylchloride (0.0648 mmol, 11.5 $\mu$L) were successively added. The solution was stirred at RT for 3h, and then it was concentrated. The residue was dissolved in MeOH and subjected to purification by HPLC, affording the ester compound as a white solid (17.9 mg, 0.0257 mmol), Purity by HPLC>95%, M+H$^+$ 696.24. LiOH 1N aq, (0.25 mmol, 257 $\mu$L) was added to the ester dissolved in THF:MeOH (2:1). The reaction was stirred at 50 °C for 1.5h prior to the addition of acetic acid (0.98 mmol, 53 $\mu$L). The solution was concentrated. The residue was dissolved in DCM and washed with water; the aqueous phase was acidified to pH 5 and then extracted with dichloromethane and ethyl acetate. The combined organic phases were dried over $Na_2SO_4$ and concentrated, affording the title compound as a white solid (7.1 mg, 0.01 mmol), Purity by HPLC>98%, M+H$^+$ 668.19.

Example 224



1-{[1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(3-phenyl-thioureido)-pyrrolidine-2-carbonyl}-amino)-2-vinyl-cyclopropanecarboxylic acid (224)

To a stirred solution of compound 218 (30 mg, 0.054 mmol) in acetonitril (3 mL), TEA (0.0648 mmol, 9 $\mu$L) and phenylthioisocyanate (0.0648 mmol, 7.8$\mu$L) were successively added .The solution was stirred at RT for 16h, and then it was

concentrated. The residue was dissolved in MeOH and subjected to purification by HPLC, affording the ester compound as a white solid (22.7mg, 0.0328mmol), Purity by HPLC>95%, $M+H^+$ 691.2. LiOH 1N aq, (0.33 mmol, 328 $\mu$lL) was added to the ester dissolved in THF:MeOH (2:1). The reaction was stirred at 50 °C for 2.5h prior to the addition of acetic acid (0.98 mmol, 53 $\mu$L). The solution was concentration. The residue was dissolved in dichloromethane and washed with water, the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $Na_2SO_4$ and concentrated, affording the title compound as a white solid (7.2 mg, 0.01 mmol), Purity by HPLC>98%, $M+H^+$ 663.26.

Assays

The compounds of the invention are conveniently assayed for activity against the NS3 protease of flavivirus such as HCV using conventional in vitro (enzyme) assays or cell culture assays.

A useful assay is the Bartenshlager replicon assay disclosed in EP 1043399. An alternative replicon assay is described in WO 03064416.

A convenient enzyme assay involving the inhibition of full-length hepatitis C NS3 is essentially as described in Poliakov, 2002 Prot Expression & Purification 25 363 371. Briefly, the hydrolysis of a depsipeptide substrate, Ac-DED(Edans)EEAbuψ[COO]ASK(Dabcyl)-$NH_2$ (AnaSpec, San José, USA), is measured spectrofluorometrically in the presence of a peptide cofactor, KKGSVVIVGRIVLSGK, as described by Landro, 1997 Biochem 36 9340-9348. The enzyme (1 nM) is incubated in a buffer such as 50 mM HEPES, pH 7.5, 10 mM DTT, 40% glycerol, 0.1% n-octyl-β-D-glucoside, with 25 μM cofactor and inhibitor at say 30 °C for 10 min, whereupon the reaction is initiated by addition of substrate, typically 0.5 μM substrate. Inhibitors are typically dissolved in DMSO, sonicated for 30 s and vortexed. The solutions are generally stored at –20°C between measurements.

An alternative enzyme assay is described in WO 0399316 and employs an HCV NS3/4A protease complex FRET peptide assay. The purpose of this in vitro assay is to measure the inhibition of HCV NS3 protease complexes, derived from the BMS, H77C or J416S strains, as described below, by compounds of the present invention. This assay provides an indication of how effective compounds of the present invention would be in inhibiting HCV proteolytic activity.

Serum is taken from an HCV-infected patient. An engineered full-length cDNA template of the HCV genome (BMS strain) was constructed from DNA fragments obtained by reverse transcription-PCR (RT-PCR) of serum RNA and using primers selected on the basis of homology between other genotype Ia strains. From the determination of the entire genome sequence, a genotype I a was assigned to the HCV isolate according to the classification of Simmonds et al. (See P Simmonds, KA Rose, S Graham, SW Chan, F McOmish, BC Dow, EA Follett, PL Yap and H Marsden, J.Clin. Microbiol., 31(6), 1493-1503 (1993)). The amino acid sequence of the nonstructural region, NS2-5B, was shown to be >97% identical to HCV genotype Ia (H77C) and 87% identical to genotype Ib (J4L6S). The infectious clones, H77C (I a genotype) and J4L6S (I b genotype) can be obtained from R. Purcell (NIH) and the sequences are published in Genbank (AAB67036, see Yanagi,M., Purcell,R.H., Emerson,S.U. and Bukh. Proc. Natl. Acad. Sci. U.S.A. 94 (16) 8738-8743 (1997); AF054247, see Yanagi,M., St Claire,M., Shapiro,M., Emerson,S.U., Purcell,R.H. and Bukhj, Virology 244 (1), 161 (1998)).

The BMS, H77C and J4L6S strains are used for production of recombinant NS3/4A protease complexes. DNA encoding the recombinant HCV NS3/4A protease complex (amino acids 1027 to 1711) for these strains were manipulated as described by P. Gallinari et al. (see Gallinari P, Paolini C, Brennan D, Nardi C, Steinkuhler C, De Francesco R. Biochemistry. 38(17):562032, (1999)). Briefly, a three-lysine solubilizing tail was added at the 3'-end of the 3 0 NS4A coding region. The cysteine in the P1 position of the NS4A-NS4B cleavage site (amino acid 1711) was changed to a glycine to avoid the proteolytic cleavage of the lysine tag.

Furthermore, a cysteine to serine mutation can be introduced by PCR at amino acid position 1454 to prevent the autolytic cleavage in the NS3 helicase domain. The variant DNA fragment can be cloned in the pET21b bacterial expression vector (Novagen) and the NS3/4A complex can be expressed in Escherichia coli strain BL21 (DE3) (Invitrogen) following the protocol described by P. Gallinari et al. (see Gallinari P, Brennan D, Nardi C, Brunetti M, Tomei L, Steinkuhler C, De Francesco R., J Virol. 72(8):6758-69 (1998)) with modifications. Briefly, NS3/4A expression can be induced with 0.5mM Isopropyl beta-D thiogalactopyranoside (IPTG) for 22hr at 20'C. A typical fermentation (I0 l) yields approximately 80g of wet cell paste. The cells are resuspended in lysis buffer (IO mL/g) consisting of 25mM N-(2Hydroxyethyl)Piperazine-N'-(2-Ethane Sulfonic acid) (HEPES), pH7.5, 20% glycerol, 5OOmM Sodium Chloride (NaCl), 0.5% Triton-X100, I ug/mL lysozyme, 5mM Magnesium Chloride (MgCl2), I ug/mL Dnasel, 5mM beta-Mercaptoethanol (BME), Protease inhibitor - Ethylenediamine Tetraacetic acid (EDTA) free (Roche), homogenized and incubated for 20 mins at VC. The homogenate is sonicated and clarified by ultra-centrifugation at 235000 g for 1 hr at 4'C.

Imidazole is added to the supernatant to a final concentration of 15mM and the pH adjusted to 8. The crude protein extract is loaded on a Nickel Nitrilotriacetic acid (Ni-NTA) column pre-equilibrated with buffer B (25n-tM 2 0 HEPES, pH8 20% glycerol, 5OOmM NaCl, 0.5% Triton-XIOO, 15mM imidazole, 5mM BME). The sample is loaded at a flow rate of lmL/min. The column is washed with 15 column volumes of buffer C (same as buffer B except with 0.2% Triton-X100). The protein is eluted with 5 column volumes of buffer D (same as buffer C except with 200mM imidazole).

NS3/4A protease complex-containing fractions are pooled and loaded on a desalting column Superdex-S200 pre-equilibrated with buffer D (25MM HEPES, pH7.5, 20% glycerol, 3OOmM NaCl, 0.2% Triton-XIOO, IOmM BME). Sample is loaded at a flow rate of lmUmin. NS3/4A protease complex3 0 containing fractions are pooled and concentrated to approximately 0.5mg/mL. The purity of the NS3/4A protease complexes, derived from the BMS, H77C and J4L6S strains, are typically judged to

be greater than 90% by SDS-PAGE and mass spectrometry analyses.

The enzyme is generally stored at -80'C, thawed on ice and diluted prior to use in assay buffer. The substrate used for the NS3/4A protease assay, is conveniently RET S 1 (Resonance Energy Transfer Depsipeptide Substrate; AnaSpec, Inc. cat # 22991)(FRET peptide), described by Taliani et al. in Anal. Biochem. 240(2):6067 (1996). The sequence of this peptide is loosely based on the NS4A/NS4B natural cleavage site except there is an ester linkage rather than an amide bond at the cleavage site. The peptide substrate is incubated with one of the three recombinant NS3/4A complexes, in the absence or presence of a compound of the present invention, and the formation of fluorescent reaction product was followed in real time using a Cytofluor Series 4000. Useful reagents are as follow: HEPES and Glycerol (Ultrapure) can be obtained from GIBCO-BRL. Dimethyl Sulfoxide (DMSO) is obtained from Sigma. Beta-Mercaptoethanol is obtained from Bio Rad.

Assay buffer: 50m.M HEPES, pH7.5; 0. 15M NaCl; 0. I% Triton; 15 % Glycerol; 10mM BME. Substrate: 2 uM final concentration (from a 2mM stock 2 0 solution in DMSO stored at -20'C). HCV NS3/4A type Ia (Ib), 2-3 nM final concentration (from a 5uM stock solution in 25mM HEPES, pH7.5, 20% glycerol, 300m.M NaCl, 0.2% Triton-X100, 10mM BME). For compounds with potencies approaching the assay limit, the assay can be made more sensitive by adding 50 ug/mL BSA to the assay buffer and/or reducing the end protease concentration to 300 pM.

The assay is conveniently performed in a 96-well polystyrene black plate from Falcon. Each well contains 25ul NS3/4A protease complex in assay buffer, 50ul of a compound of the present invention in 10% DMSO/assay buffer and 25ul substrate in assay buffer. A control (no compound) is also prepared on the same assay plate. The enzyme complex is mixed with compound or control solution, typically for 1 min before initiating the enzymatic reaction by the addition of substrate. The assay plate is generally read immediately using a spectrophotometer such as a Cytofluor Series 4000 (Perspective Biosysterns). The instrument is conveniently set to read an

emission of 340nm and excitation of 490nm at 25'C. Reactions are generally followed for approximately 15 minutes.

The percent inhibition can be calculated with the following equation.

$$100.- [(dF_{inh}/dF_{con})X100]$$

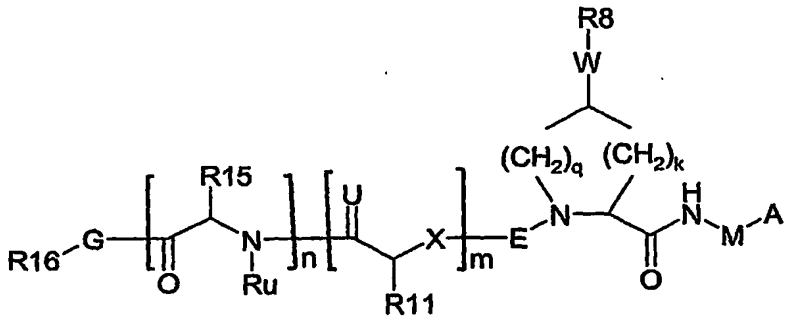
where dF is the change in fluorescence over the linear range of the curve. A nonlinear curve fit is applied to the inhibition-concentration data, and the 50% effective concentration ($IC_{50}$) is calculated by the use software such as Excel XI-fit software using the equation:

$$y=A+((B-A)/(1+((C/x)^D))).$$

Various compounds of the invention exemplified above displayed $IC_{50}$s in the range 1nM to 6.9 micromolar and $ED_{50}$s in the sub-micromolar to micromolar range.

Claims

1. A compound of the formula I:




wherein

A is $COOR^1$, $CONHSO_2R^2$, $CONHR^3$, or $CR^4R^{4'}$ wherein;

$R^1$ is hydrogen, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl;

$R^2$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl;

$R^3$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $-OC_1$-$C_6$alkyl, $-OC_0$-$C_3$alkylcarbocyclyl, $-OC_0$-$C_3$alkylheterocyclyl;

$R^4$ is =O, halo, amino, or OH;

$R^{4'}$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl; wherein

$R^2$, $R^3$, and $R^{4'}$ are each optionally substituted with from 1 to 3 times with halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-$R_b$, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-NHSO$_p$Rb, Y-S(=O)$_p$Rb, Y-S(=O)$_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

where Y is independently a bond or $C_1$-$C_3$ alkyl;

Ra is independently H or $C_1$-$C_3$ alkyl;

Rb is independently H, $C_1$-$C_6$ alkyl, $C_0$-$C_3$ alkylcarbocyclyl or $C_0$-$C_3$heterocyclyll;

p is independently 1 or 2;

M is $CR^7R^{7'}$ or NRu;

$R^7$ is $C_1$-$C_6$alkyl, $C_1$-$C_3$alkyl $C_3$-$C_7$cycloalkyl, or $C_2$-$C_6$alkenyl, any of which is optionally substituted with 1-3 halo atoms, amino or –SH;

$R^{7'}$ is H or taken together with $R^7$ to form a $C_3$-$C_6$ cycloalkyl ring optionally substituted with $R^{7'a}$ wherein;

$R^{7'a}$ is $C_1$-$C_6$ alkyl, $C_3$-$C_5$cycloalkyl, $C_2$-$C_6$ alkenyl or J; any of which may be optionally substituted with halo;

q is 0 to 3 and k is 0 to 3; where q+k ≥1;

W is -$CH_2$-, -O-, -OC(=O)H-, -OC(=O)-, -S-, –NH-, -$NR^{8'}$ , -$NHSO_2$-, -NHC(=O)NH- or -NHC(=O)-, -NHC(=S)NH-;

$R^8$ is a ring system containing 1 or 2 saturated or unsaturated rings each of which has 4-7 ring atoms and 0 to 2 hetero atoms selected from S, O and N, the ring system being optionally spaced from W by a $C_1$-$C_3$ alkyl group; or $R^8$ is $C_1$-$C_6$ alkyl, any of which $R^8$ groups can be optionally mono, di, or tri substituted with $R^9$, wherein

$R^9$ is independently halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb; wherein the carbocyclyl or heterocyclyl is optionally substituted with $R^{10}$; wherein

$R^{10}$ is $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_6$alkoxy, amino optionally mono- or di- substituted with $C_1$-$C_6$-alkyl, sulfonyl, ($C_1$-$C_3$ alkyl)sulfonyl, $NO_2$, OH, SH, halo, haloalkyl, carboxyl, amide, ($C_1$-$C_3$alkyl)amide;

$R^{8'}$ is H, $C_1$-$C_3$alkyl;

E is -C(=O)-, -C(=S)-, -$S(=O)_2$-, -S=O-, -C=N-Rf;

Rf is H, -CN, -C(=O)NRaRb; -C(=O)$C_1$-$C_3$alkyl;

X is –NRx- where Rx is H, or $C_1$-$C_5$alkyl; or in the case where where E is –(C=O) X can also be -O- or -NRjNRj-;

wherein one of Rj is H or $C_1$-$C_3$alkyl, the other is H or J;

$R^{11}$ is H, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

when $R^{7'}$ taken together with $R^7$ forms a $C_3$-$C_6$ cycloalkyl, then one of Rj, Rx, Ry or $R^{11}$ can also be J;

J, if present, is a 3 to 10-membered saturated or unsaturated alkylene chain extending from the $R^7/R^{7'}$ cycloalkyl to Rj, Rx, Ry or $R^{11}$ to form a macrocycle, which chain is optionally interrupted by one to three heteroatoms independently selected from: -O-, -S- or -$NR^{12}$- wherein 0 to 3 carbon atoms in the chain are optionally substituted with $R^{14}$; wherein;

$R^{12}$ is H, $C_1$-$C_6$ alkyl, $C_3$-$C_6$cycloalkyl, or $COR^{13}$;

$R^{13}$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl;

$R^{14}$ is independently selected from H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, $C_1$-$C_6$ alkoxy, hydroxy, halo, amino, oxo, thio, or $C_1$-$C_6$ thioalkyl;

Ru is independently H or $C_1$-$C_3$ alkyl;

m is 0 or 1; n is 0 or 1;

U is O or is absent;

$R^{15}$ is H, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$ alkyl, $C_0$-$C_3$-alkylheterocyclyl, $C_0$-$C_3$carbocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

G is –O-, -NRy-, –NRjNRj- ;

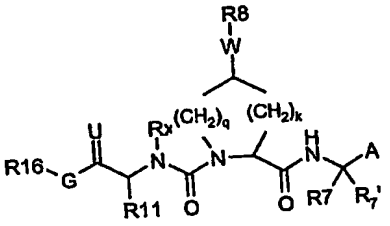
Ry is H, $C_1$-$C_3$ alkyl or J;

$R^{16}$ is H; or $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylcarbocyclyl, $C_0$-$C_3$alkylheterocyclyl, $NH_2CO$-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_p$Rb, Y-$S(=O)_p$Rb, Y-$S(=O)_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

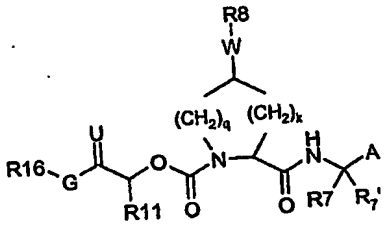
or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound according to claim 1 wherein M is $CR^7R^{7'}$.

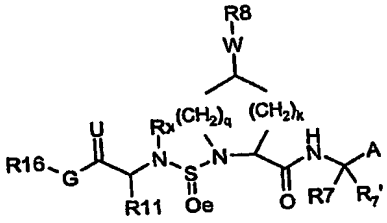
3. A compound according to claim 2 with the formula Iea-Iee:



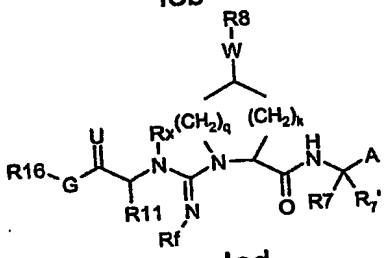
Iea



Ieb



Iec



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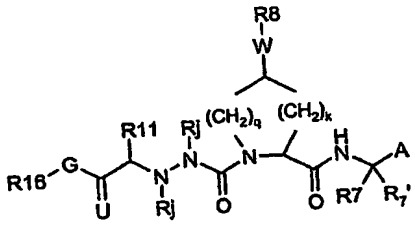
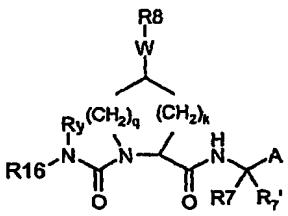


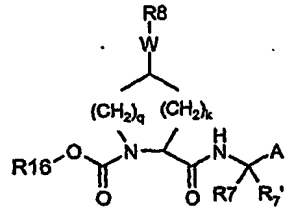
Iee

where e is 1 or 2.

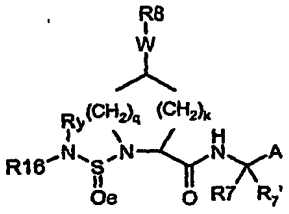
4. A compound according to claim 2 with the formula Ifa-Ife



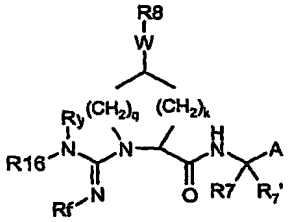
Ifa



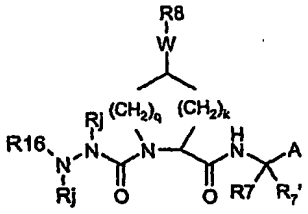
Ifb



Ifc



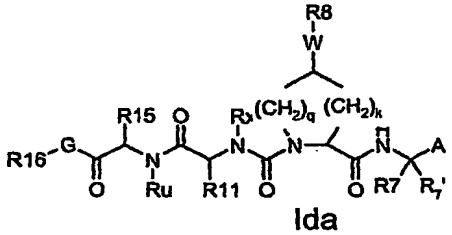
Ifd



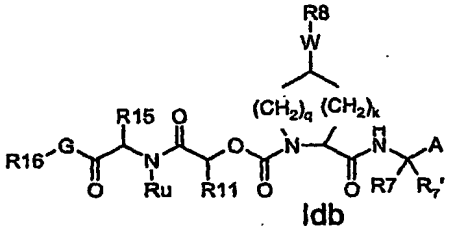
Ife

where e is 0 to 2.

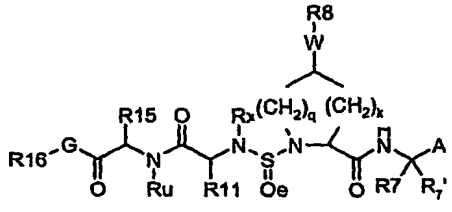
5. A compound according to claim 2, with the formula Ida-Idd



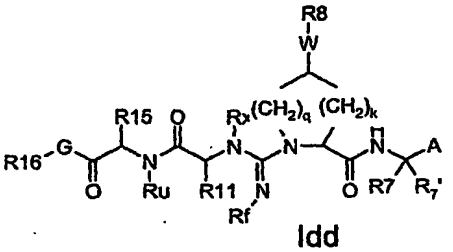
Ida



Idb



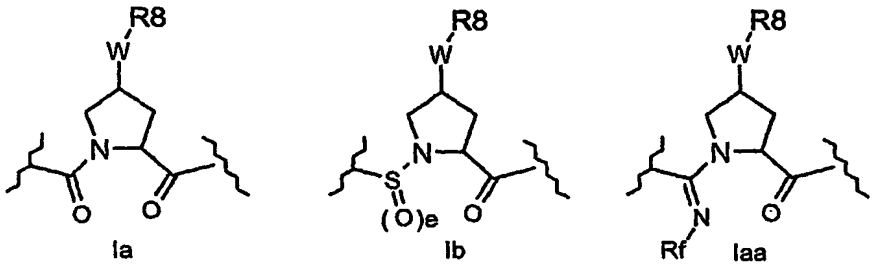
Idc



Idd

6. A compound according any preceding claim, wherein X is –NRx-.

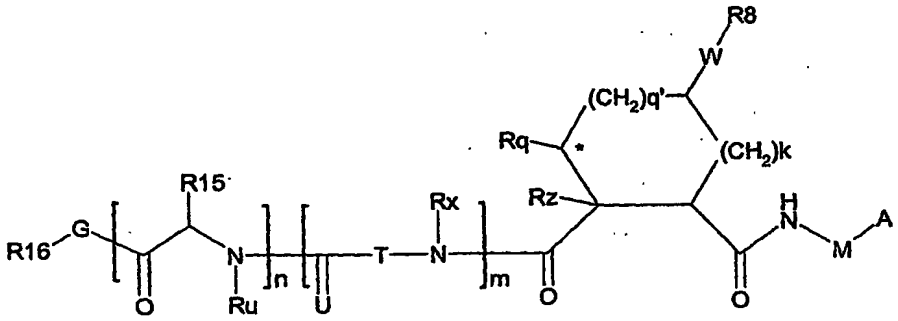
7. A compound according to any preceding claim with the partial structure Ia, Ib or Iaa:




where e is 1 or 2

8. A compound according to any preceding claim, wherein E is –C(=O)- or –C=NRf.

9. A compound with the formula VI




VI

wherein

$R^7$, $R^{7'}$, $R^8$, $R^{11}$, $R^{15}$, $R^{16}$, Rj, Ru, Rx, Ry, A, G, k, m, n, M, U, W are as defined in claim 1;

q' is 0 or 1;

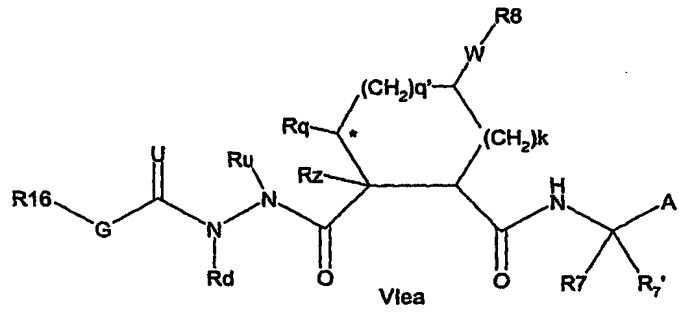
Rz is H, or together with the asterisked carbon forms an olefinic bond;

Rq is H or $C_1$-$C_4$-alkyl;

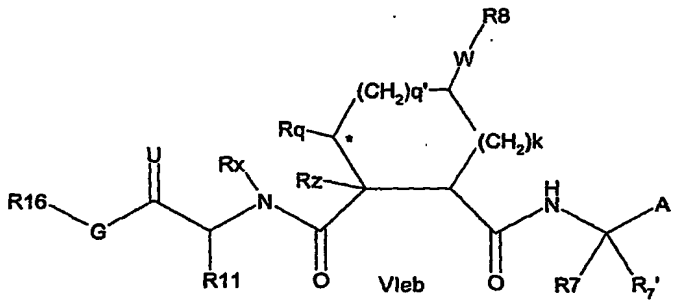
T is -CHR$^{11}$- or –NRd-, where Rd is H or $C_1$-$C_3$alkyl;
in the case where $R^7$ taken together with $R^{7'}$ forms a $C_3$-$C_6$ cycloalkyl, one of Rd, Rj, Rx, Ry or $R^{11}$ can be J;
J is, if present, a 5 to 10 membered saturated or unsaturated alkylene chain extending from the $R^7$/$R^{7'}$ cycloalkyl to Rd, Rj, Rx, Ry or $R^{11}$ to form a macrocycle, which chain is otherwise as defined in claim 1;
and pharmaceutically acceptable salts and prodrugs thereof.

10 A compound according to claim 9, where M is $CR^7R^{7'}$.

11. A compound according to claim 10 with the formula VIea or VIeb:

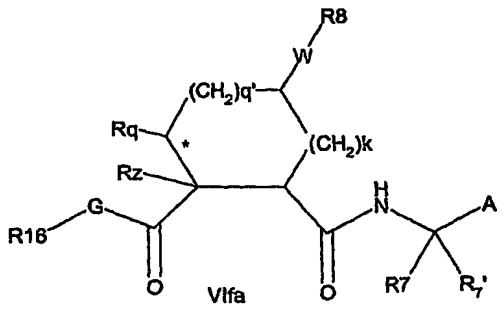



VIea



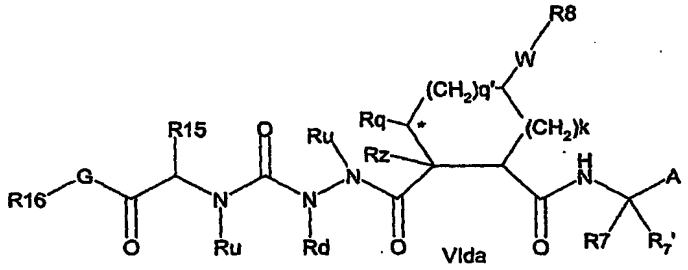

VIeb

12. A compound according to claim 10 with the formula VIfa.

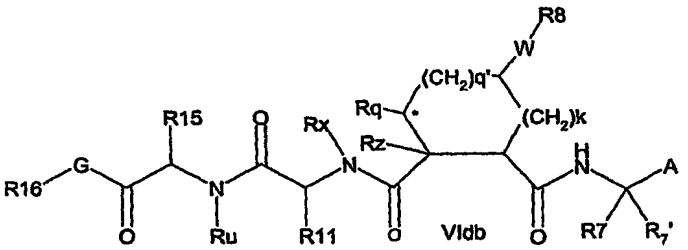



VIfa

13. A compound according to claim 10 with the structure VIda or VIdb



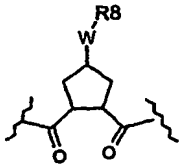

VIda



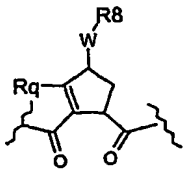

VIdb

14. A compound according to any of claims 9 to 13, wherein Rz is H.

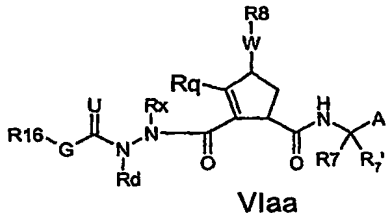
15. A compound according to any of claims 9 to 14 with the partial structure:



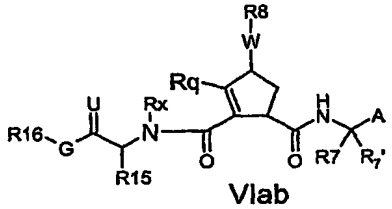

16. A compound according to any of claims 9 to 14 with the partial structure



17. A compound according to claim 16, with the formula VIaa or VIab:

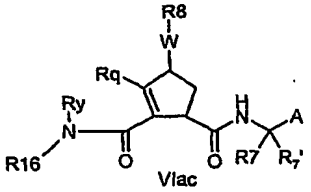


VIaa

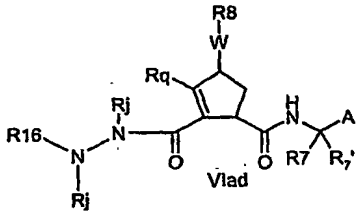


VIab

18. A compound according to claim 16, with the formula VIac or VIad:

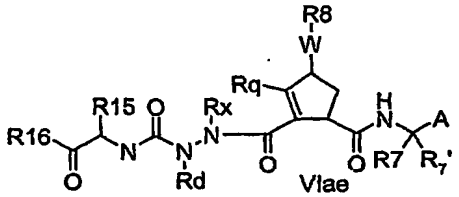


VIac

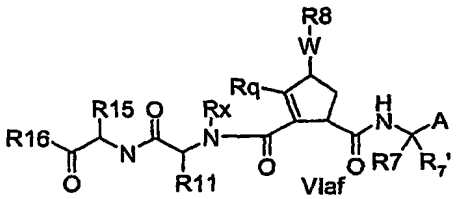


VIad

19. A compound according to claim 16, with the formula VIae-VIaf



VIae



VIaf

20. A compound according to any of claims 9 to 19, where Rq is H or methyl.

21. A compound according to any preceding claim wherein $R^{7'}$ is H and $R^7$ is n-ethyl, n-propyl, cyclopropylmethyl, cyclobutylmethyl, 2,2-difluoroethyl, or mercaptomethyl.

22. A compound according to claim 21, wherein $R^7$ is n-propyl or 2,2-difluoroethyl.

23. A compound according to any of claims 1 to 20 wherein $R^7$ and $R^{7'}$ together define a spiro-cyclopropyl or spiro-cyclobutyl ring, both optionally mono or di-substituted with $R^{7'a}$ wherein;

$R^{7'a}$ is $C_1$-$C_6$ alkyl, $C_3$-$C_5$cycloalkyl, or $C_2$-$C_6$ alkenyl, any of which is optionally substituted with halo or J.

24. A compound according to claim 23 wherein the ring is a spiro-cyclopropyl ring substituted with $R^{7'a}$ wherein;

$R^{7'a}$ is ethyl, vinyl, cyclopropyl, 1- or 2-bromoethyl, 1-or 2-fluoroethyl, 2-bromovinyl or 2-fluorethyl.

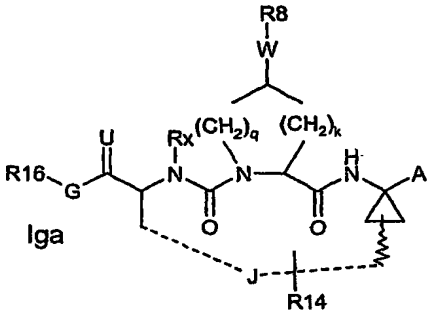
25 A compound according to claim 23, wherein J is a 3 to 8-membered saturated or unsaturated alkylene chain optionally containing one to two heteroatoms independently selected from: -O-, -S- or -$NR^{12}$- , wherein $R^{12}$ is H, $C_1$-$C_6$ alkyl, such as methyl, or -C(=O)$C_1$-$C_6$ alkyl, such as acetyl.

26. A compound according to claim 25 wherein J is a 5 to 8-membered saturated or unsaturated, all carbon alkylene chain.

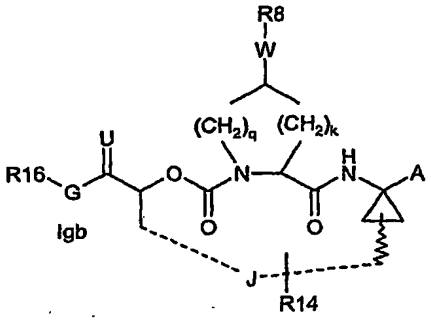
27. A compound according to claim 25 or 26 wherein J is saturated or mono-unsaturated.

28. A compound according to claim 25, 26 or 27, wherein J is substituted with $R^{14}$, wherein $R^{14}$ is H or $C_1$-$C_6$alkyl.

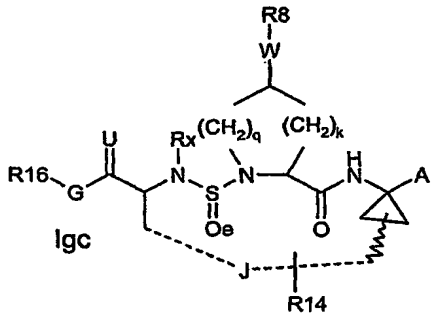
29. A compound according to claims 25-28 with the formula Iga-Igf



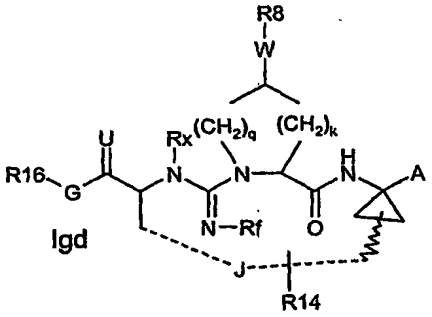

Iga



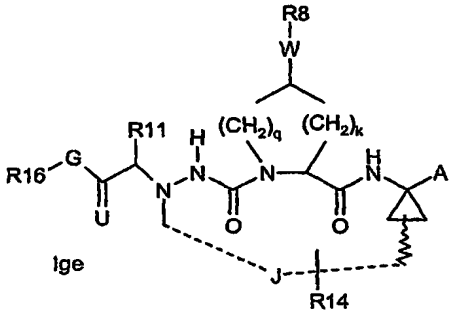

Igb



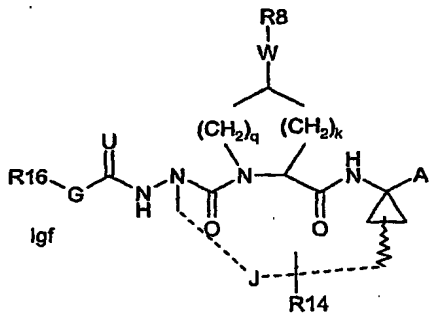

Igc




Igd



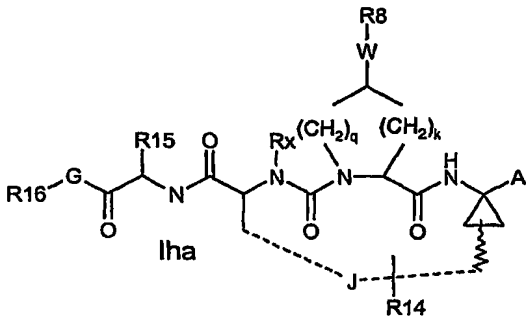

Ige



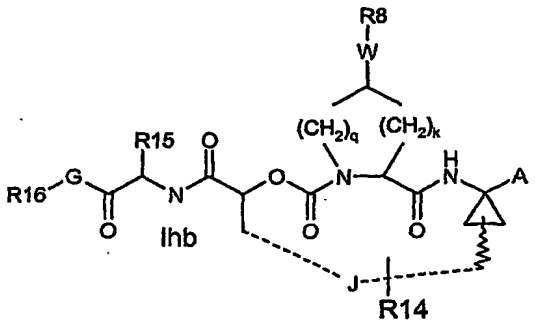

Igf

where e is 1 or 2.

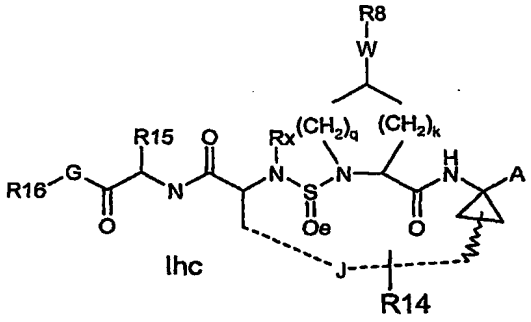
30. A compound according to claims 25 to 28 with the structure Iha-Ihf.



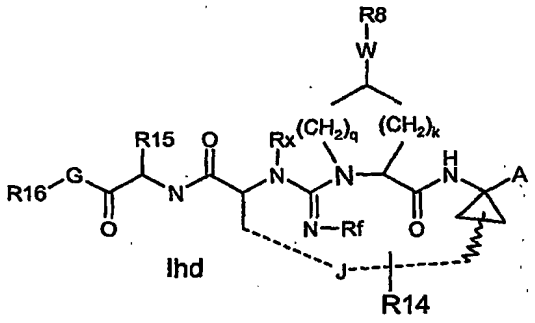

Iha



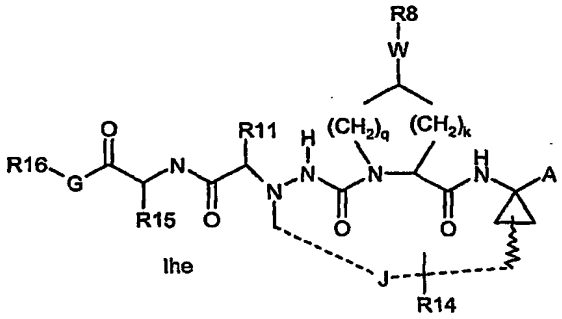

Ihb



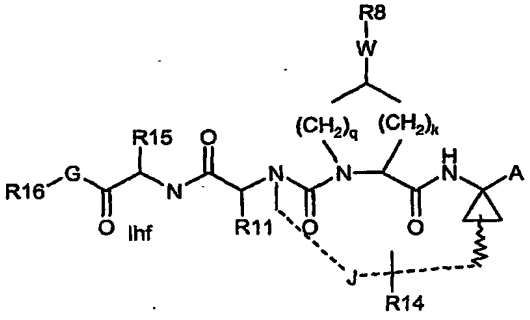

Ihc




Ihd



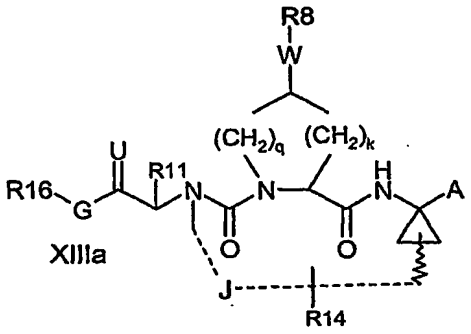

Ihe



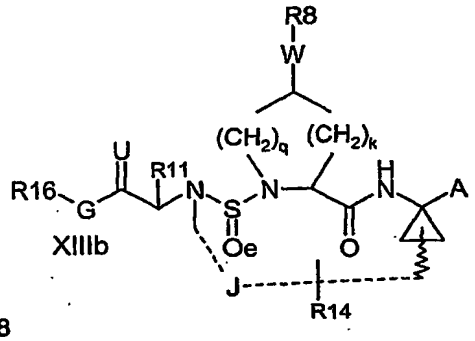

Ihf

5

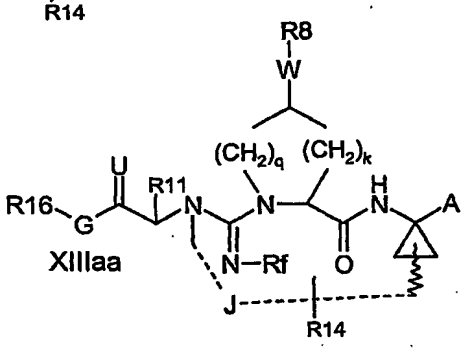
31. A compound according to claims 25 to 28 with the formula XIIIa, XIIIaa or XIIIb




XIIIa

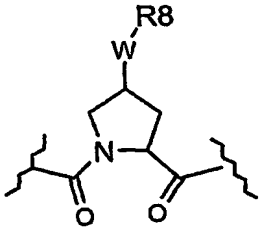



XIIIb

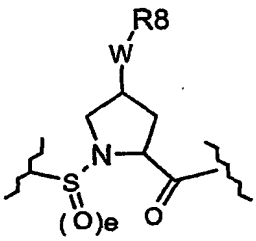



XIIIaa

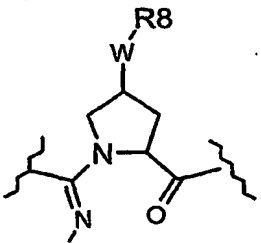
32. A compound according to claim 29, 30 or 31 with the partial structure




Ia

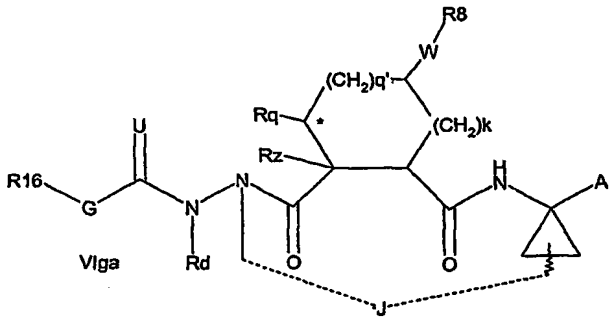


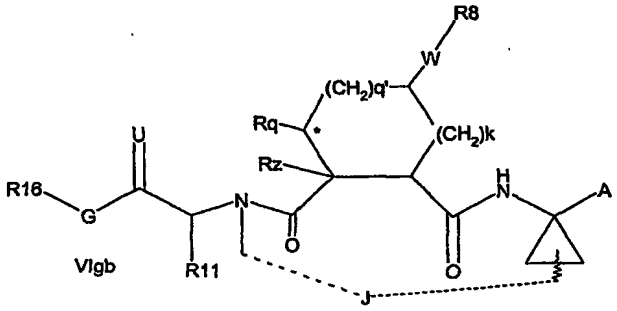

Ib

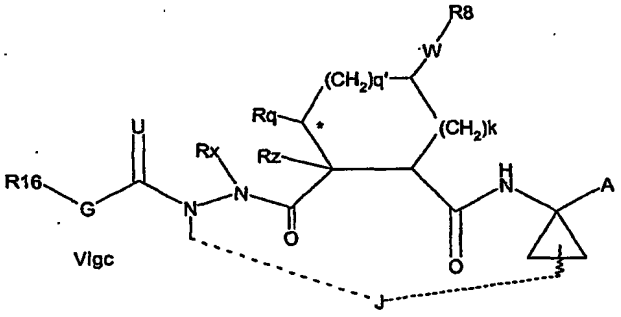



Ic

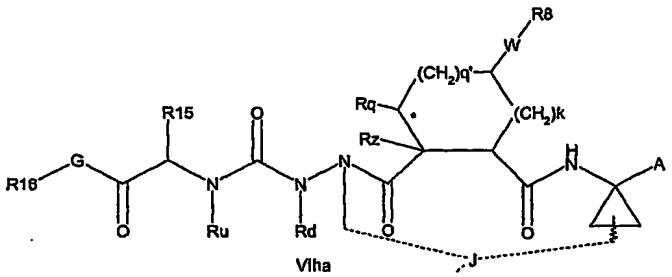
33. A compound according to claims 25 to 28 with the formula VIga-VIgc



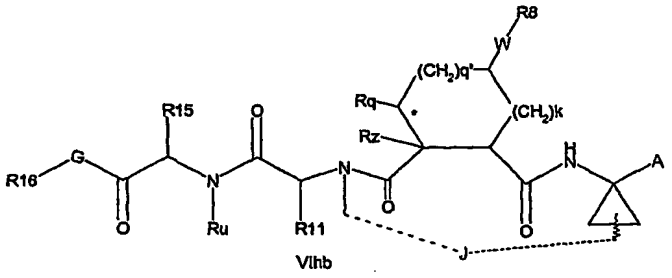



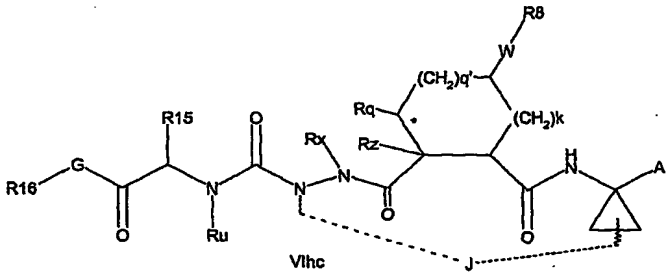
34. A compound according to claims 25 to 28 with the formula VIha-VIhc:




VIha

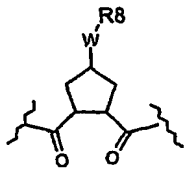



VIhb

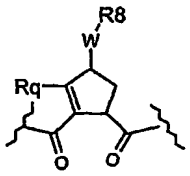



VIhc

35. A compound according to claim 33 or 34 with the partial structure:



36. A compound according to claim 33 or 34 with the partial structure:




37. A compound according to claim 36, wherein Rq is methyl or H.

38. A compound according to claims 1 to 37, wherein A is $CONHR^3$.

39. A compound according to claim 38, wherein $R^3$ is $C_0$-$C_3$alkylaryl, $C_0$-$C_3$alkylhetroaryl, $OC_0$-$C_3$alkylaryl or $OC_0$-$C_3$alkylhetroaryl any of which is optionally substituted.

40. A compound according to claim 39, wherein $R^3$ is $C_0$-$C_3$alkylaryl or $C_0$-$C_3$alkylhetroaryl any of which is optionally substituted.

41. A compound according to claims 1 to 37, wherein A is $CONHSO_2R^2$.

42. A compound according to claim 41, wherein $R^2$ is optionally substituted $C_1$-$C_6$ alkyl, preferably methyl.

43. A compound according to claim 41, wherein $R^2$ is optionally substituted $C_3$-$C_7$cycloalkyl, preferably cyclopropyl.

44. A compound according to claim 41 wherein $R^2$ is optionally substituted $C_0$-$C_6$alkylaryl, preferably optionally substituted phenyl.

45. A compound according to claims 1 to 37, wherein A is $COOR^1$.

46. A compound according to claim 45, wherein $R^1$ is H or $C_1$-$C_6$ alkyl

47 A compound according to claim 45 wherein $R^1$ is hydrogen, methyl, ethyl, or tert-butyl.

48 A compound according to any preceding claim, wherein W is -OC(=O)NH-, -OC(=O)-, -NH-, -$NR^{8'}$-, -$NHS(O)_2$-or -NHC(=O)-.

49 A compound according to claim 48 wherein W is –OC(=O)NH- or –NH-

50 A compound according to claim 48 or 49 wherein $R^8$ is optionally substituted $C_0$-$C_3$-alkylcarbocyclyl or $C_o$-$C_3$-alkylheterocyclyl.

51 A compound according to claims 1 to 47 wherein W is -S- or preferably –O-.

52 A compound according to claim 51 wherein $R^8$ is $C_0$-$C_3$alkylaryl, or $C_o$-$C_3$alkylhetroaryl either of which is optionally mono, di, or tri substituted with $R^9$, wherein;

$R^9$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$alkoxy, $NO_2$, OH, halo, trifluoromethyl, amino or amido optionally mono- or di-substituted with $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylaryl, $C_o$-$C_3$alkylhetroaryl, carboxyl, aryl or heteroaryl being optionally substituted with $R^{10}$; wherein

$R^{10}$ is $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_6$alkoxy, amino optionally mono- or di-substituted with $C_1$-$C_6$alkyl, $C_1$-$C_3$ alkyl amide), sulfonyl$C_1$-$C_3$alkyl, $NO_2$, OH, halo, trifluoromethyl, carboxyl, or hetroaryl.

53 A compound according to claim 52 wherein $R^9$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$alkoxy, amino, di-($C_1$-$C_3$ alkyl)amino, $C_1$-$C_3$alkylamide, aryl or hetroaryl, the aryl or hetroaryl being optionally substituted with $R^{10}$; wherein

$R^{10}$ is $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_6$alkoxy, amino, mono- or di-$C_1$-$C_3$ alkylamino, amido, $C_1$-$C_3$ alkylamide, halo, trifluoromethyl, or hetroaryl.

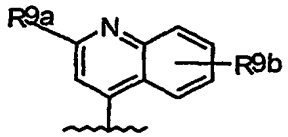
54. A compound according to claim 53, wherein, $R^{10}$ is $C_1$-$C_6$alkyl, $C_1$-$C_6$alkoxy, amino optionally mono- or di substituted with $C_1$-$C_3$ alkyl, amido, $C_1$-$C_3$-alkylamide, halo, or hetroaryl.

55. A compound according to any preceding claim wherein $R^{10}$ is methyl, ethyl, isopropyl , tert-butyl, methoxy, chloro, amino optionally mono- or di substituted with $C_1$-$C_3$ alkyl, amido, $C_1$-$C_3$alkylamide, or $C_1$-$C_3$alkyl thiazole.

56 A compound according to claims 52 to 55, wherein $R^8$ is 1-naphthylmethyl, 2-naphthylmethyl, benzyl, 1-naphthyl, 2-naphthyl, or quinolinyl any of which is unsubstituted, mono, or disubstituted with $R^9$ as defined.

57 A compound according to claim 56 wherein $R^8$ is 1-naphthylmethyl, or quinolinyl any of which is unsubstituted, mono, or disubstituted with $R^9$ as defined.

58 A compound according to claim 56 wherein $R^8$ is:



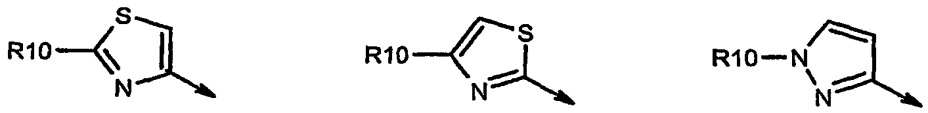

wherein $R^{9a}$ is $C_1$-$C_6$ alkyl; $C_1$-$C_6$alkoxy; thio$C_1$-$C_3$alkyl; amino optionally substituted with $C_1$-$C_6$alkyl; $C_0$-$C_3$alkylaryl; or $C_0$-$C_3$ alkylheteroaryl, $C_0$-$C_3$ alkylheterocyclyl, said aryl, heteroaryl or heterocycle being optionally substituted with $R^{10}$ wherein

$R^{10}$ is $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl, $C_1$-$C_6$alkoxy, amino optionally mono- or di-substituted with $C_1$-$C_6$alkyl, amido, $C_1$-$C_3$alkyl amide; and

$R^{9b}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$-alkoxy, amino, di($C_1$-$C_3$alkyl)amino, ($C_1$-$C_3$alkyl) amide, $NO_2$, OH, halo, trifluoromethyl, carboxyl.

59 A compound according to claim 58, wherein $R^{9a}$ is aryl or heteroaryl, either of which is optionally substituted with $R^{10}$ as defined.

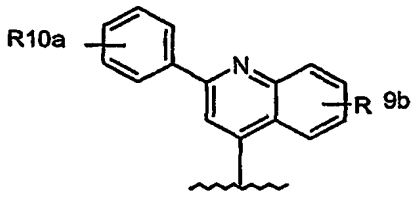
60 A compound according to 59, wherein $R^{9a}$ is selected from the group consisted of:



wherein $R^{10}$ is H, $C_1$-$C_6$alkyl, or $C_0$-$C_3$alkyl-$C_3$-$C_6$cycloalkyl, amino optionally mono- or di-substituted with $C_1$-$C_6$alkyl, amido, ($C_1$-$C_3$alkyl)amide.

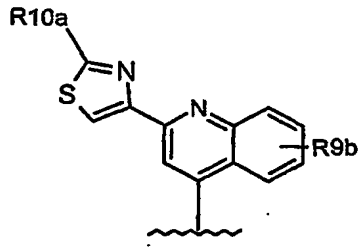
61. A compound according to claim 59, wherein $R^{9a}$ is optionally susbstituted phenyl.

62. A compound according to claim 58, wherein $R^8$ is:



wherein $R^{10a}$ is H, $C_1$-$C_6$alkyl; $C_1$-$C_6$alkoxy; or halo; and $R^{9b}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$-alkoxy, amino, di($C_1$-$C_3$alkyl)amino, ($C_1$-$C_3$alkyl)amide, $NO_2$, OH, halo, trifluoromethyl, carboxyl.

63. A compound according to claim 58, wherein $R^8$ is:



wherein $R^{10a}$ is H, $C_1$-$C_6$alkyl, or $C_0$-$C_3$alkyl-$C_3$-$C_6$cycloalkyl, amino optionally mono- or di-substituted with $C_1$-$C_6$alkyl, amido, ($C_1$-$C_3$ alkyl)amide, heteroaryl or heterocyclyl; and $R^{9b}$ is $C_1$-$C_6$ alkyl, $C_1$-$C_6$-alkoxy, amino, di($C_1$-$C_3$ alkyl)amino, ($C_1$-$C_3$ alkyl)amide, $NO_2$, OH, halo, trifluoromethyl, or carboxyl.

64. A compound according to any claim 58-63, wherein $R^{9b}$ is $C_1$-$C_6$-alkoxy, preferably methoxy.

65. A compound according to any preceding claim, wherein Rx is methyl or preferably H.

66. A compound according to any preceding claim, wherein $R^{11}$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$ alkyl$C_3$-$C_7$ cycloalkylyl, $C_0$-$C_3$alkylaryl or $C_0$-$C_3$ alkylheteroaryl, any of which is optionally substituted with hydroxy, halo, amino, $C_1$-$C_6$alkoxy, $C_1$-$C_6$thioalkyl, $COOR^{14}$, carboxyl, ($C_1$-$C_6$alkoxy)carbonyl, aryl, heteroaryl or heterocyclyl;

67 A compound according to claim 66, wherein the substituent is hydroxy or $COOR^{14}$.

68. A compound according to claim 67, wherein $R^{11}$ is tert-butyl, iso-butyl, cyclohexyl, phenylethyl, 2,2-dimetyl-propyl, cyclohexylmethyl, phenylmethyl, 2-pyridylmethyl, 4-hydroxy-phenylmethyl, or carboxylpropyl.

69. A compound according to claim 68, wherein $R^{11}$ is tert-butyl, iso-butyl, or cyclohexyl.

70. A compound according to claim 1 or 9, wherein Ru is methyl or preferably H.

71. A compound according to any preceding claim, wherein $R^{15}$ is $C_1$-$C_6$alkyl, $C_3$-$C_7$cycloalkyl, $C_0$-$C_3$alkyl$C_3$-$C_7$cycloalkyl any of which can be optionally substituted.

72. A compound according to claim 71, wherein $R^{15}$ is cyclohexyl, cyclohexylmethyl, tert-butyl, iso-propyl, or iso-butyl.

73. A compound according to claim 1 or 9, wherein m is zero and T is absent.

74. A compound according to any preceding claim, wherein G is –NRy- .

75. A compound according to claim 74, wherein Ry is methyl or preferably H.

76. A compound according to claim 74 or 75, wherein $R^{16}$ is a nitrogen containing heterocycle which is N-linked to G.

77. A compound according to claim 76, wherein Ry is J.

78. A compound according to any of claims 1 or 9, wherein G is –NRjNRj-.

79. A compound accrding to claim 78, wherein m and n are zero.

80. A compound according to claim 78 or 79, wherein each Rj is H.

81. A compound according to claim 78 or 79, wherein one Rj is H and the other is J.

82. A compound according to any preceding claim, wherein $R^{16}$ is $C_1$-$C_6$alkyl, $C_0$-$C_3$alkylheterocyclyl, $C_0$-$C_3$alkylcarbocyclyl, any of which is optionally substituted with hydroxy, halo, amino, or $C_1$-$C_6$alkoxy.

83. A compound according to claim 82, wherein $R^{16}$ is methyl.

84. A compound according to claim 82, wherein $R^{16}$ is 2-indanol, indanyl, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, cyclohexylmethyl, 2,3-methylenedioxybenzyl, cyclohexyl, benzyl, 2-pyridylmethyl, cyclobutyl, iso-butyl, n-propyl, or 4-methoxyphenylethyl.

85. A pharmaceutical composition comprising a compound as defined in any preceding claim and a pharmaceutically acceptable carrier therefore.

86. A pharmaceutical composition according to claim 85, further comprising an additional HCV antiviral, selected from nucleoside analogue polymerase inhibitors, protease inhibitors, ribavirin and interferon.

87. Use of a compound as defined in any of claims 1-84 in the manufacture of a medicament for the prophylaxis or treatment of flavivirus infections, including HCV.

Abstract of the Disclosure

Peptidomimetic compounds are described which inhibit the NS3 protease of the hepatitis C virus (HCV). The compounds comprise a novel linkage between a carbocyclic or heterocyclic P2 unit and those portions of the inhibitor more distal to the cleavage site, which linkage which reverses the orientation of peptidic bonds on the distal side relative to those proximal to the cleavage site.

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